NEURO

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ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-2-115

Review

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Volume 2 : Issue 2
Article Ref. #: 1000NOJ2115

Article History
Received: September 9th, 2015
Accepted: September 19th, 2015
Published: September 21st, 2015

Citation
Riccardi VM. Current utilization of mast cell stabilizers for preemptive treatment of NF1 neurofibromas. *Neuro Open J.* 2015; 2(2): 67-73. doi: 10.17140/NOJ-2-115

Current Utilization of Mast Cell Stabilizers for Preemptive Treatment of NF1 Neurofibromas

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ABSTRACT

The morbidity and mortality of Neurofibromatosis type I (NF1) are both largely related to the person's neurofibroma burden. That burden can presently be minimized by mast cell stabilizers, with ketotifen as the one most frequently considered for NF1 patients in the published literature. Here, I review pertinent clinical and research publications to 1) document the *rationale* for using mast cell blockers in NF1, 2) consider the NF1 clinical *impact* of mast cell blockers, 3) document the relative *safety* and very modest *expense* of (at least some) mast cell blockers, and 4) suggest that the data are sufficiently robust to *support* the regular, if not *routine use of mast cell blockers to treat NF1*, particularly in children, while the NF1 neurofibroma burden is the least it will be. The rationale for these salutary results have been established by histopathology, *Nf1*+/- mouse models, a series of open-label and double-blind protocols, , compelling case reports and a series of patients who have afforded their own self-determined mast cell stabilizer treatment (most often ketotifen). In addition, in the intervening 20-plus years since the first formal protocol publications, the positive treatment results have never been refuted or contradicted. The results of the mast-cell-stabilizing treatment are designed to keep the NF1 neurofibroma burden and its consequences at their minimums, in effect preempting NF1 neurofibroma initiation and progression as much as possible.

KEYWORDS: Neurofibromatosis 1; NF1; Neurofibroma; Mast cells; Pain; Itching; Pruritus; Ketotifen.

ABBREVIATIONS: DPN: Diffuse Plexiform Neurofibromas; NF1: Neurofibromatosis type I; FDA: Food and Drug Administration.

INTRODUCTION

The morbidity and mortality of NF1 are directly and indirectly related to the person's neurofibroma burden. The person with more and/or larger neurofibromas is at higher risk. Most persons with NF1 are born absent neurofibromas of any type. However, I estimate that between 5% and 15% of NF1 persons have one or more congenital neurofibromas. These are properly referred to as Diffuse Plexiform Neurofibromas (DPN)[1,2] and more technically as epineurial neurofibromas.[1] In addition, almost all NF1 persons are also at risk for the later development of cutaneous neurofibromas (endoneurial neurofibromas)[1] and some NF1 persons are at risk for subcutaneous and nodular plexiform neurofibromas (both of which are perineurial neurofibromas).[1] The latter are likely associated with higher mortality[3,4] and they are especially common in persons with NF1 on the basis of a "whole gene deletion."[5,6]

For the most part, the routine approach to NF1 has been to wait for progression of the NF1 neurofibroma burdens to have major, serious clinical consequences and then use very expensive medications that often have serious side-effects and uncertain abilities to stop or reverse the neurofibroma's progression. In this presentation, I suggest greater reliance on pre-

ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-2-115

emption – minimize the initiation and progression of these mass lesions.

The NF1 neurofibromas can have direct and indirect adverse consequences, precisely as neurofibromas, depending on absolute size, adjacent structures and infiltration into surrounding tissue. Endoneurial (cutaneous) neurofibromas usually first appear in the teenage years, ultimately often accounting for hundreds, even thousands of individual lesions, varying in size from a few grams[7] to several kilograms.[7] At any size they are almost always cosmetically compromising and are the sites of localized itching, pain and tenderness. Perineurial (subcutaneous and nodular plexiform) neurofibromas may occur at any age and are often a source of substantial pain and focal neurological deficits. Nodular plexiform neurofibromas are often paraspinal at multiple sites.[1,8,9] In addition, a minimum 10% of NF1 patients will experience malignant transformation of one or more plexiform neurofibromas, perineurial or epineurial (DPN), the malignant tumor usually a sarcoma, most often a neurofibrosarcoma.[10-12] While it has not been proven that a mast cell blocker preemption approach decreases the malignant transformation risk, it seems likely – even compelling – that an arrested neurofibroma is less likely to realize this transformation. Can there be a better reason for attempting to arrest the growth of NF1 neurofibromas?

REVIEW

Pathologists have known for decades that mast cells are an intrinsic element of neurofibromas, whether or not NF1 is present.[13-21] In some instances, NF1 neurofibroma mast cells have been quantified and there is consistently an excess compared to normal tissue.[22,23] However, no attempts seem to have been made to identify the tissue source or detailed nature of the NF1 neurofibroma's mature mast cells, for example, tryptase or chymase predominance.[24,25] Likewise, no efforts have been made to distinguish the immature mast cell[26,27] newly arrived to the incipient neurofibroma in contrast to the "mature," more or less neurofibroma-specific mast cell. Targeting the immature mast cell may be a key to arresting the incipient or very early stage neurofibroma.[28] In any event, numerous pathologists established a role for mast cells in neurofibroma pathogenesis.

Respecting both the pathology data just noted and consistent with NF1 patient reports that likely sites of neurofibroma development were heralded by focal intense itching,[12,29-31] a symptom well-known to indicate mast cell infiltration, Riccardi began emphasizing a key role for mast cells and cell-cell interactions in NF1 neurofibroma pathogenesis.[30,32] A key part of the proffered schema was consideration that the early stages of the neurofibroma are more like wound-healing dysplasia than neoplasia *sensu strictu*.[7,33,34]

Most early (and even many present-day) neurofibroma investigators presumed automatically that a neurofibroma is a tumor from the outset, with a somatic mutation in the normal *NF1* allele (second hit) in a Schwann cell being the literal "cause" of the NF1 neurofibroma.[35-38] This myopic approach ignores the cogent possibility that the initial dynamics of NF1 neurofibroma formation were more related to wound-healing, the wound providing a cellular and extra-cellular milieu affording an increased likelihood of the second hit (incubator effect).[8] Trauma (mechanical, biochemical, hypoxic) and wound-healing became a focus of NF1 neurofibroma pathogenesis in the very early 1980's.[39-46]

Along the way, in 1988, Giorno, et al.,[47] documented that human NF1 neurofibroma fibroblasts (a major portion of the lesion) incorporate mast cell granules into their cytoplasm, consistent with the work of others.[48] These results were also consistent with the massive data generated by the Wade Clapp University of Indiana group using *Nf1* mutant mice.[49-60] They professed and nurtured the notion that "mast cells are necessary, but not sufficient" to generate *Nf1*+/- neurofibromas. One published commentary on that work noted the compatibility of this mouse model with the Riccardi approach.[51] And a 2009 publication[61] showed that the mast cell blocker, tranilast, impaired the ability of *Nf1*+/- mice neurofibroma to progress.

Further indication that mechanical trauma initiated mouse *Nf1*+/- neurofibromas was established by A.C. Lloyd's group.[62] Wound-healing was also emphasized by others.[41,45,63-65] The Lloyd group's article just cited also established that normal (*Nf1*+/+) mast cells were as efficient as *Nf1*+/- mast cells in generating and sustaining mouse *Nf1*+/- neurofibromas. In other words, it is likely that the mast cell *per se* and its ordinary functions contribute to human NF1 neurofibroma initiation and progression. The NF1 mast cell as a therapeutic target of drugs aimed at normal mast cells, as, for example, in asthma and other mast-cell- associated disorders, was and is thereby even more compelling.

All of these developments were in the context of Riccardi's publications documenting that ketotifen (Zaditen®), in both open-label and double-blind protocols, had obvious benefits in treating NF1 neurofibromas. As early as 1987, such benefits were published in the *Archives of Dermatology*.[66] Additional data were published in 1990 and 1993.[33,67] In the 20-plus years since their publication, these data and the conclusions derived therefrom have been casually challenged once,[68,69] but never refuted or contradicted. The published benefits of NF1 ketotifen treatment included 1) a *decrease in the itching, pain and tenderness* associated with neurofibromas of all three types, especially for the endoneurial (cutaneous) neurofibromas and subcutaneous perineurial neurofibromas; 2) a *decrease in the rate of appearance* of cutaneous neurofibromas; 3) a *decrease in the rate of enlargement* ("growth") of all types of neurofibromas; 4) a major *decrease in intra-operative small-vessel hemorrhage* in plexiform neurofibromas; and 5) a consistent declaration of *improvement in the NF1 person's overall sense of well-being*. Parenthetically, this latter phenomenon has been noted in patients treated with ketotifen to minimize surgical scars.[70] In 1998, for

three German NF1 patients were reported[71] to have the same salutary results from ketotifen treatment as reported by Riccardi.

In 2015, I reported the results of 30 years of ketotifen treatment of an NF1 patient from age three months.[72] At age 30, his skin was universally free of any mature neurofibromas. Instead, there was only the monotonous presence of "early," small and flat cutaneous neurofibromas. It was as though these neurofibromas had been arrested and maintained in this very early phase of neurofibroma development. In addition, the patient's right ankle DPN was much smaller than would have been expected without treatment. At about the same time, I established *NFormation*, an online venue to report on advances in NF1 research (www.medconsumer.com). Included were a series of American, European and South American NF1 persons who were undergoing or had undergone self-determined treatment with ketotifen or an alternative mast cell blocker. The consistency of the self-reported results was impressive, both within the self-determined treatment group and when compared with the three protocol-based reports noted above. Finally, the combined data are sufficiently robust to have instigated the already-begun preemptive treatment of a one year old child with NF1 for whom there is expectation of a high cutaneous neurofibroma burden.

Although ketotifen has not been approved by the American Food and Drug Administration (FDA) other than for eyedrops (Zaditor®), there are multiple active investigational ketotifen protocols in the USA and elsewhere to study this drug's influence on minimizing fibrosing conditions[73-75] and excessive scarring in surgical and other wounds.[76-80] Ketotifen is also used extensively world-wide for asthma, atopic dermatitis, helminthic infections, and various eating disorders, among others.[81,82] With such extensive clinical usage, its relative safety is well established. It is relatively inexpensive, with costs per tablet in the range of 15 cents or so. It is now available in generic form and it remains to be established that all of the available brands are equivalent to Zaditen®, the only preparation with which I have extensive personal experience. It also should be noted that the FDA's failure to approve ketotifen was based on that agency's presumption of poor efficacy for treating asthma. Specifically, ketotifen did not have toxicity or adverse effects that contributed to denial of FDA approval.

One of the conditions sometimes very effectively treated with ketotifen is systemic mastocytosis.[25,83-85] This pronouncement brings up the probability that NF1 may be a form of mastocytosis, a consideration raised earlier by myself[86] and others.[87] Ultimately, these and many other considerations will be relevant to the long-term role of ketotifen and other mast cell blockers, for example, the identification of effective biomarkers[88] and the influence of vitamin D congeners.[89] However, our concerns presently are on if and how soon mast cell blockers – especially ketotifen – are made available to *all* persons with NF1. This issue is especially critical for Americans, given the lack of FDA approval of ketotifen, the literal and figurative fuel for elaborating the arguments propounded here.

CONCLUSION

Ketotifen and likely similar mast cell blockers have the potential to reduce drastically the NF1 neurofibroma burden on a world-wide basis. Given the data provided herein, it is not clear why this potential has been overlooked, ignored or dismissed. I can only hope that these few words will make this treatment strategy immediately available to at least some of the earth's estimated two million or more persons alive with NF1 today.

CONFLICTS OF INTEREST

I, the sole author of this manuscript, have no conflicts of interest to declare. Specifically, I have no financial interests of any sort, direct or indirect, with any for-profit organization or semblance thereto. I will realize no financial or other compensation consequent to or otherwise associated with this manuscript.

ACKNOWLEDGMENTS

Thanks to the many NF1 patients and their families for their participation in the formal and informal protocols and their cooperation in finalizing the data. "The Neurofibromatosis Institute" is simply an alternative name for my clinical, research and publication activities; it has no legal status.

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