

Case report of a recalcitrant allergic contact eczema successfully treated with Teriflunomide

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Key Words: Case-report; Eczema; Teriflunomide; Multiple Sclerosis

Abstract:

Allergic contact dermatitis (ACD) is a type IV, delayed-type reaction caused by skin contact with low-molecular-weight organic chemicals and metal ions that activate antigen-specific T cells, primarily T-helper 1 (Th1), in a sensitized individual, leading to skin eczema.

First-line treatments are based on avoidance of causal agents and topical corticosteroids /immunomodulators. In recalcitrant cases, chronic oral immunosuppressive agents may be used, but they may have serious adverse effects and do not address the immunological disfunction.

We report a case of severe ACD, unresponsive to topical or oral immunosuppressive therapy, which resolved itself after treatment with teriflunomide (TF) 14 mg/daily used for Multiple Sclerosis. TF is a once-daily oral selective and reversible dihydro-orotate dehydrogenase (DHODH) inhibitor, revealing a new treatment option for ACD.

Clinical case:

We present a case of a 61-year-old woman followed in dermatology consultation for 20 years due to an ACD. Her left leg was amputated due to a car accident, requiring the use of leg prosthesis and crutches. Three days after she began using the prosthesis, she developed intense pruritus and vesiculo-erythematous lesions at the stump and palms. Later these lesions became lichenified, with hyperkeratosis and fissures (fig. 1). Patch tests revealed positivity for nickel sulphate 5% (+), Thiuram mix 1% (++), Colophony 20% (++), Thimerosal 0.1% (++), Balsam of Peru 25% (+), Epoxy resin 1% (+), Cobalt Chloride 1% (+). Prosthesis material was also positive (++). A skin biopsy of the stump was also compatible with the diagnosis of ACD.

Therefore, the diagnosis of allergic contact dermatitis towards the prosthesis material and crutches was pre-emptive.

Despite a change of prosthesis material and use of barrier creams, topical corticosteroids (medium- and high-potency) and oral corticosteroids, thalidomide and cyclosporine, the clinical response was not satisfactory and/or lasting.

In March of 2017, at 59 years old, she was observed at our hospital's outpatient Neurology clinic with a transverse myelitis. She described four distinct previous episodes of neurological deficits with spontaneous recovery, compatible with optic neuritis (29 and 53 years old) and transverse myelitis (40 and 53 years old). She had right relative afferent pupillary defect, right hemiparesis and right hemisensory loss below T2. MRI showed multiple T2 and fluid-attenuated inversion recovery (FLAIR) hyperintense white matter lesions (periventricular, subcortical, justacortical and dorsal spinal cord) and right optic nerve atrophy. Oligoclonal bands in cerebrospinal fluid were present. Clinical and imaging criteria for relapsing-remitting multiple sclerosis were fulfilled. (Thompson et al., 2018) She started TF 14mg qd in October

2017. TF is a first-line disease-modifying therapy approved for relapsing-remitting multiple sclerosis (Biotti & Ciron, 2018)

After starting this treatment, the skin lesions were completely resolved within two weeks despite the contact with the allergens (fig 2.) and no other immunosuppressor was added. After 12 months she remains disease free, without report of significant adverse events.

Discussion:

This case reveals a new therapeutic approach to ACD.

ACD occurs after an initial sensitization phase (Martin, 2015). The initial pro-inflammatory cytokines milieu is essential for this process. The stimulation of toll-like receptors (TLR) by danger-associated molecular patterns (DAMPs) or ATP, and signalling through NFkB and MAPK pathways activates the immune system leading to full activation of Langerhans cells (McFadden, Puangpet, Basketter, Dearman, & Kimber, 2013), that migrate from the skin to lymph nodes and present T cell epitopes allowing the naïve T cell priming (Esser & Martin, 2017).

The sensitization simultaneously generates antigen-specific skin resident memory CD8⁺T cells (T_{RM}), and lymph node central memory CD8⁺T cells (T_{CM}) from the same common naïve T cell precursor (Gaide et al., 2015).

During elicitation phase, T_{RM} are activated, proliferate and cause an immediate response with rapid release of IFNγ and IL-17A (Schmidt et al., 2017), while T_{CM} will migrate later to skin and cause delayed and attenuated responses (Gaide et al., 2015).

Teriflunomide (TF) is a first-line disease-modifying therapy approved for relapsing-remitting multiple sclerosis (Biotti & Ciron, 2018), with less adverse effects than leflunomide. The mechanism of action of TF is not fully established.

TF blocks de novo pyrimidine synthesis by specific non-competitive, reversible inhibition of the mitochondrial enzyme DHODH (Bruneau et al., 1998; Rückemann et al., 1998). This enzyme is highly expressed in antigen-induced proliferative lymphocytes, consequently the blockade of

pyrimidine synthesis interrupts the cell cycle in S-phase, exerting a cytostatic effect (Bar-Or, Pachner, Menguy-Vacheron, Kaplan, & Wiendl, 2014). This effect appears to be more pronounced in T-cells bearing T-cell receptors (TCRs) with a high affinity for a presented peptide antigen, leaving lower-avidity T-cells available for normal responses to pathogens(Bar-Or et al., 2014).

Cells such as resting lymphocytes or gastrointestinal mucosa, that do not proliferate in response to activation, are spared because they can meet requirements of pyrimidine through the salvage pathway [(Bar-Or et al., 2014)].

Tolerogenic responses in ACD are also essential. The crosstalk between CD4⁺ regulatory T (Treg) cells and epidermal Langerhans cells (LC) induce tolerance mainly through IL-10 production (Igyarto et al., 2009; Luckey et al., 2012) and through ATP signalling blocking(Mahnke et al., 2017). Studies with Leflunomide (LF), which is converted in vivo to TF, showed an increase in the immunosuppressive cytokine, TGF-beta 1, an inducer of Treg cells(Cao et al., 1996). Moreover, LF also enhances production of IL-10 in LPS-stimulated microglia and since microglia and epidermal LC have the same origin, it is possible that LF has a similar effect on LC (Korn, Magnus, Toyka, & Jung, 2004). Additionally, inhibition of DHODH also suppresses NF-KB associated kinases(Manna, Mukhopadhyay, & Aggarwal, 2000), including IFN- γ gene, crucial to the elicitation and sensitization phase, as mentioned.

These potential benefits were shown in a mouse model of allergic contact dermatitis. The oral administration of LF abrogated the response in already-sensitized mice; inhibited sensitization when administered concomitantly with dinitrofluorobenzene (DNFB) and prevented an allergic response during subsequent sensitization phase, even in the absence of LF (Weigmann et al., 2006). This suggests the generation of regulatory T cells, which can confer long-lasting protection. LF was also useful in some case reports of eczematous dermatitis, usually after failure of other immunosuppressors (Boyd, 2013)

Studies with patients and healthy volunteers treated with TF also points towards an immunomodulatory, rather than immunosuppressive mechanism of action, since immune

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responses to both recall and neoantigen vaccinations, though mildly reduced, remained sufficient to afford seroprotection (Bar-Or et al., 2014).

In line with this findings, pooled data from four placebo-controlled studies and extensions in MS showed that majority of adverse events with TF were of mild-to-moderate intensity, self-limited, and infrequently resulted in discontinuation of therapy, being the most common reason for treatment discontinuation elevated plasma liver enzymes. Infections were not reported with greater frequency in patients treated with teriflunomide(Comi et al., 2016). Comparative data with other drugs is scarce. A double-blind trial comparing clinical safety of LF vs Methotrexate (MTX) in patients with rheumatoid arthritis found that both share similar treatment-related adverse events (diarrhoea, nausea, alopecia, rash, headache, and elevated plasma liver enzyme levels), but withdrawn because of elevated plasma liver enzymes and drug-related deaths from pulmonary was more common in MTX group (21 vs 8 and 2 vs 0, respectively)(Emery et al., 2000).

Additionally, TF might have a “cleaner” action mode compared with LF, since TF is already the active metabolite and there is no production of secondary metabolites probably linked to some secondary effects observed with LF.

Conclusion

In conclusion, TF might represent a new oral treatment option for recalcitrant ACD, especially when the contact with the culprit allergen cannot be avoided and other first-line treatments have failed or are not tolerated. TF appear to favour immunomodulation over immunosuppression, in a way that might re-induce tolerance, however it's acting mode and posology in ACD is not completely understood. Data about long-term safety is reassuring, but comparative studies are missing. Although the results are promising, this is a single report and more studies must be done to understand the true impact of this new drug in dermatology.

Bar-Or, A., Pachner, A., Menguy-Vacheron, F., Kaplan, J., & Wiendl, H. (2014). Teriflunomide and Its

- Mechanism of Action in Multiple Sclerosis. *Drugs*, 74(6), 659–674.
- Biotti, D., & Ciron, J. (2018). First-line therapy in relapsing remitting multiple sclerosis. *Revue Neurologique*, 174(6), 419–428.
- Boyd, A. S. (2013). Successful treatment of recalcitrant eczematous dermatitis with leflunomide. *Journal of the American Academy of Dermatology*, 69(3), e148–e149.
- Bruneau, J. M., Yea, C. M., Spinella-Jaegle, S., Fudali, C., Woodward, K., Robson, P. A., ... Ruuth, E. (1998). Purification of human dihydro-orotate dehydrogenase and its inhibition by A77 1726, the active metabolite of leflunomide. *The Biochemical Journal*, 336 (Pt 2(Pt 2), 299–303.
- Cao, W. W., Kao, P. N., Aoki, Y., Xu, J. C., Shorthouse, R. A., & Morris, R. E. (1996). A novel mechanism of action of the immunomodulatory drug, leflunomide: augmentation of the immunosuppressive cytokine, TGF-beta 1, and suppression of the immunostimulatory cytokine, IL-2. *Transplantation Proceedings*, 28(6), 3079–3080.
- Comi, G., Freedman, M. S., Kappos, L., Olsson, T. P., Miller, A. E., Wolinsky, J. S., ... Leist, T. P. (2016). Pooled safety and tolerability data from four placebo-controlled teriflunomide studies and extensions. *Multiple Sclerosis and Related Disorders*, 5, 97–104.
- Emery, P., Breedveld, F. C., Lemmel, E. M., Kaltwasser, J. P., Dawes, P. T., Gömör, B., ... Loew-Friedrich, I. (2000). A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology*, 39(6), 655–665.
- Esser, P. R., & Martin, S. F. (2017). Pathomechanisms of Contact Sensitization. *Current Allergy and Asthma Reports*, 17(12), 83.
- Gaide, O., Emerson, R. O., Jiang, X., Gulati, N., Nizza, S., Desmarais, C., ... Kupper, T. S. (2015). Common clonal origin of central and resident memory T cells following skin immunization. *Nature Medicine*, 21(6), 647–653.
- Igyarto, B. Z., Jenison, M. C., Dudda, J. C., Roers, A., Müller, W., Koni, P. A., ... Kaplan, D. H. (2009). Langerhans cells suppress contact hypersensitivity responses via cognate CD4 interaction and langerhans cell-derived IL-10. *Journal of Immunology (Baltimore, Md. : 1950)*, 183(8), 5085–5093.
- Korn, T., Magnus, T., Toyka, K., & Jung, S. (2004). Modulation of effector cell functions in experimental autoimmune encephalomyelitis by leflunomide--mechanisms independent of pyrimidine

depletion. *Journal of Leukocyte Biology*, 76(5), 950–960.

- Luckey, U., Schmidt, T., Pfender, N., Romer, M., Lorenz, N., Martin, S. F., ... Steinbrink, K. (2012). Crosstalk of regulatory T cells and tolerogenic dendritic cells prevents contact allergy in subjects with low zone tolerance. *Journal of Allergy and Clinical Immunology*, 130(3), 781–797.e11.
- Mahnke, K., Useliene, J., Ring, S., Kage, P., Jendrossek, V., Robson, S. C., ... Enk, A. H. (2017). Down-Regulation of CD62L Shedding in T Cells by CD39 + Regulatory T Cells Leads to Defective Sensitization in Contact Hypersensitivity Reactions. *Journal of Investigative Dermatology*, 137(1), 106–114.
- Manna, S. K., Mukhopadhyay, A., & Aggarwal, B. B. (2000). Leflunomide suppresses TNF-induced cellular responses: effects on NF-kappa B, activator protein-1, c-Jun N-terminal protein kinase, and apoptosis. *Journal of Immunology*, 165(10), 5962–5969.
- Martin, S. F. (2015). Immunological mechanisms in allergic contact dermatitis. *Current Opinion in Allergy and Clinical Immunology*, 15(2), 124–130.
- McFadden, J. P., Puangpet, P., Basketter, D. A., Dearman, R. J., & Kimber, I. (2013). Why does allergic contact dermatitis exist? *British Journal of Dermatology*, 168(4), 692–699.
- Rückemann, K., Fairbanks, L. D., Carrey, E. A., Hawrylowicz, C. M., Richards, D. F., Kirschbaum, B., & Simmonds, H. A. (1998). Leflunomide inhibits pyrimidine de novo synthesis in mitogen-stimulated T-lymphocytes from healthy humans. *The Journal of Biological Chemistry*, 273(34), 21682–21691.
- Schmidt, J. D., Ahlström, M. G., Johansen, J. D., Dyring-Andersen, B., Agerbeck, C., Nielsen, M. M., ... Bonefeld, C. M. (2017). Rapid allergen-induced interleukin-17 and interferon- γ secretion by skin-resident memory CD8 + T cells. *Contact Dermatitis*, 76(4), 218–227.
- Thompson, A. J., Banwell, B. L., Barkhof, F., Carroll, W. M., Coetzee, T., Comi, G., ... Cohen, J. A. (2018). Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *The Lancet. Neurology*, 17(2), 162–173.
- Weigmann, B., Jarman, E. R., Sudowe, S., Bros, M., Knop, J., & Reske-Kunz, A. B. (2006). Induction of Regulatory T Cells by Leflunomide in a Murine Model of Contact Allergen Sensitivity. *Journal of Investigative Dermatology*, 126(7), 1524–1533



