Target/therapies for chronic recurrent erythema nodosum leprosum

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Abstract:
A Type 2 lepra reaction or erythema nodosum leprosum is an anticipated complication in the lepromatous spectrum of leprosy cases. It is an example of an immune complex-mediated complement activated disease (Type III hypersensitivity reaction). Hence, we tried to target the inflammatory mediators and the mental stressors for the possible management strategies.

Keywords:
Antidiabetic, erythema nodosum leprosum, lepra reaction, pharmacology, stress, targets

Introduction

Erythema nodosum leprosum (ENL) is a troublesome, and difficult to manage immunological entity seen in bacilli positive intermediate borderline lepromatous and the polar lepromatous leprosy. ENL presents both as acute or chronic episodes. The acute episodes occur at multiple time point till the bacilli are removed from the body.[1,2] In an Indian cohort study, only <10% of patients had a single episode, while around 62.5% had chronic occurring ENL.[3] Various manifestations of ENL include generalized, cutaneous, and peripheral nerve involvement. The name derived from its cutaneous manifestations that occurred as a widespread crops of lesions that are erythematous, inflamed subcutaneous nodules, and/or papules. They appear superficially or rarely deep that weans off periodically.[3] The severe forms such as bullous, pustular, ulcerated, and necrotic forms have also been routinely described. ENL nodules in several circumstances lead to fibrosis that causes irreversible scarring.[3] The nerve involved sometimes present with painful may be enlarged with functional impairment. The ENL patients mostly present with generalized illness due to immune complex activation causing high-grade fever and toxemia. Transient proteinuria and edema of hands and feet may also occur in the severe category. In the eye, iridocyclitis can occur in some cases and may be sight-threatening and early intervention is always mandatory.[3] The other findings such as scrotal swelling, hepatomegaly, splenomegaly, lymph node involvement, polyarthritus, and inflammation of the fingers with osteoporosis are well-recognized and documented.

Possible Targets

The areas for the possible targets include the mental stressors and the inflammatory mediators [Figure 1].

Inflammatory mediators as targets
Various serological markers have been identified in the pathology of ENL reaction. This includes tumor necrosis factor alpha (TNF-α), interleukins (IL-6, IL-7, and IL-17F), matrix metalloproteinases-9, phenolic glycolipids-1, chemokine ligand-11, and alpha-1-acid glycoprotein[4] [Table 1].

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The most important mechanism by which steroids and thalidomide act is through the inhibition of TNF-α, which are found in high levels in inflammation seen in ENL reactions [Figure 2].

**Old wine in new bottle (metformin for erythema nodosum leprosum)**

**Metformin as an anti-inflammatory (tumor necrosis factor-alpha inhibition)**

Many in vitro studies [Table 2] proved the anti-inflammatory action of metformin focusing on TNF-α inhibition. These inhibitory effects were mediated through different pathways. The various pathways showing inhibition of TNF-α are mammalian target of rapamycin – signaling pathway in human keratinocytes in psoriasis,[6] Activating ATF3 induction in murine macrophage,[6] inhibiting early inflammatory mediators of human monocytes growth response factor 1[7] and inhibiting nuclear factor-kappa b (NF-kb) in endothelial cells.[8]

**In animal experiments**

Many in vivo studies [Table 2] also demonstrated the inhibitory role of metformin on tumor necrosis factor alpha claiming its anti-inflammatory role. The anti-inflammatory effects of metformin have been shown in a Wistar rat model of myocardial infarction where left ventricular dysfunction occurs due to myocardial inflammation and the same is reduced by metformin,[9] reduction of inflammation in murine autoimmune arthritis[10] and also in endotoxemic mice.[12]

**Clinical studies**

In recent years, around eight studies [Table 3] have shown the inhibitory role of metformin on TNF-α when they were either given as monotherapy[13,17-20] or in combination with other drugs.[14,16] The results have also shown a direct inhibitory potential in respect to dose and duration.

**Mental Stressors as Target**

The most common precipitating factors for the development of lepra reactions are well established in literatures include vaccinations, infections, multidrug therapy for leprosy, and psychological stress.[21,22] The role of the psychological component is not much evaluated by interventional drug during the management of reactions.

**Physiology of mental stressors**

It is very well-established that mental stressors in reaction patients cause activation of two important neural pathways. The one being the hypothalamic-pituitary-adrenal axis, and the other is the autonomic system. The sympathetic nervous system contributes the maximum causing the neurogenic inflammation.[23] The cutaneous structure is an important component of this established neuro-immunocutaneous-endocrine system and the emotional disturbances as reflected by anxiety and psychological distress can significantly alter the immunological status of the patient leading to intense reactions.[24]

**Drug targets**

Hence, a group of drugs targeting these mental stressor could be a good strategy to prevent the occurrences of recurrent reactions and to break the vicious cycle triggering these recurrences [Figure 1]. This helps the patients from not exposing frequently to the ill effects of anti-reactions drugs which are with major adverse effects.

**Selective serotonin re-uptake inhibitors**

In this respect, the drug “Selective Serotonin Re-uptake inhibitors, (SSRI’s)” could be a good pharmacological interventions in preventing the recurrence of lepra
reactions. In the brain, the neuronal communication happens through the chemical synapse. There are two types of regions, namely the presynaptic and postsynaptic region/cells. The presynaptic cell which releases neurotransmitters namely serotonin into the junctional gap once the signal is received. The serotonin acts on their respective receptors present on the surface of the postsynaptic cell and causes the stimulation and other underlying molecular mechanisms. During this process, almost 90% of serotonin is released from the postsynaptic receptors into the cleft and once again taken up into the presynaptic neurons by the monoamine transporters by a process of reuptake. SSRIs drugs inhibit the process of this reuptake and increase the concentration of serotonin in the synaptic cleft and helps in postsynaptic receptor stimulations.

SSRIs are a group of anti-depressants, often prescribed for depression and generalized anxiety disorder because they are safe and well tolerated.[13,15,17]

Selective serotonin re-uptake inhibitor’s - anti-inflammatory

The anti-inflammatory properties of SSRI were not only on the peripheral immune cells but also centrally on microglial cells that respond to various signals of inflammatory factors. A study by Tynan et al.,[25] evaluated the efficacy of five different SSRIs in assessing the suppression property of the drugs to a various inflammatory stimulus. The drugs, namely citalopram, sertraline, fluoxetine, fluvoxamine, and paroxetine along with one other group of SNRI drug were used. They found its role in the suppression of microglial inflammation in response to inflammatory stimulus. The study also examined their ability to alter TNF-α and found its potential in the inhibition of microglial tumor necrosis factor-α and suggesting that antidepressants have therapeutic effectiveness to their anti-inflammatory properties also. As the recent evidences also pile up with SSRI's for its additional anti-inflammatory benefits,[26] it could be a good therapeutic strategy in treating both the mental stressor as well as the reaction inflammations.

Table 3: Clinical studies showing inhibitory action of metformin on tumor necrosis factor alpha

| Studies                  | Participants | Duration (months) | Intervention group                        | Tnf-alpha value (pg/ml) | Baseline       | End          |
|--------------------------|--------------|-------------------|-------------------------------------------|-------------------------|----------------|--------------|
| Lund et al., 2008[12]    | 88           | 4                 | Metformin                                 | 3.23±1.62               | 3.04±1.35      |              |
| Derosa et al., 2010[13]  | 74           | 12                | Metformin + pioglitazone                  | 4.0±1.4                 | 3.0±0.5        |              |
| Derosa et al., 2012 (ng/ml)[14] | 83           | 12                | Metformin                                 | 2.2±0.8                 | 2.0±0.6        |              |
| Krysiak and Okopien 2012[15] | 29           | 3                 | Metformin + simvastatin                   | 314±35                  | 240±40         |              |
| McCoy et al., 2012[16]   | 12           | 3                 | Metformin                                 | 1.40±0.55               | 1.26±0.51      |              |
| Yu et al., 2012[17]      | 41           | 6                 | Metformin                                 | 16.29±2.1               | 9.56±1.7       |              |
| Derosa et al., 2013 (ng/ml)[18] | 87           | 12                | Metformin                                 | 2.3±1.0                 | 1.5±0.4        |              |
| Xu et al., 2015[19]      | 21           | 3                 | Metformin                                 | Reduced                 |                |              |

Values are given as mean±SD. SD=Standard deviation

Discussion

ENL occurs due to immune complex mediated-complement system activation. In general, in response to various stimuli, the immune cells release both the cytokines, pro-inflammatory as well as the anti-inflammatory.[20] Macrophages are activated by pro-inflammatory cytokines that promote inflammation. The anti-inflammatory cytokines help in balancing the immune system by preventing the hazardous effect of inflammation caused by pro-inflammatory cytokines.[27,28]

In a study by Hyun et al., our hypothesized drug metformin reduced the production of cytokines, namely IL (IL-1β, IL-6, TNF-α) in a dose-dependent manner and by the inhibition of protein and messenger RNA expression. In addition to its inhibiting properties, the anti-inflammatory cytokines, namely IL-4 and IL-10 protein expression were also upregulated, and it is maintained throughout.[29] Hence, the drug metformin can be used in an ENL reaction with dual benefit in a dose-dependent manner.
Circulating monocytes are attracted by chemokine and by various adhesion molecules, namely selectin (E and P), vascular cell adhesion molecule 1, intercellular adhesion molecule 1, that were expressed by endothelial cells on stimulation by TNF-α. There occurs an increase in an inflammatory response which is caused by Monocyte-derived macrophages and vascular endothelial cells by the release of various chemoattractants and the cytokines in pro-inflammation. These migrations of monocytes from the systemic vascular compartment to the site of inflammation can be inhibited by metformin.

The transcription factor namely NF-κB plays a vital role in the orchestra of various inflammatory responses. Metformin exerts its anti-inflammation in a dose-dependent manner. It reduces the synthesis of all pro-inflammatory cytokines through the suppression of IkBα phosphorylation and also the translocation of NF-κB mainly the protein p65 from the cytoplasm to the core nucleus. In pregnancy also metformin can be used safely.

Prednisolone and thalidomide have been used in ENL to suppress the severity of clinical manifestations and to provide remission. Being drugs with major side-effects, the plan for the use of alternative drugs for the treatment of ENL that down-regulate TNF production should be a logical approach in the management of reaction. In this regard, metformin seems to be safe in all the age groups and can be used for a longer duration.

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Conflicts of interest
There are no conflicts of interest.

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