СЕКЦИЯ № 2 «СОЦИАЛЬНО ЗНАЧИМЫЕ ДЕРМАТОЗЫ: ПСОРИАЗ И ОПУХОЛИ КОЖИ»

IMIQUIMOD

ĶīsisJ,Ķīse L, Zavorins A, Pētersone G
Riga Stradins University

Introduction. The lead compound of the imidazoquinoline family, imiquimod, is a nucleoside analog that was originally developed as a potential antiviral agent. Further investigations uncovered that imiquimod does not demonstrate any direct antiviral activity. However, it has been proven to be a potent immunomudulator with antitumoral properties [Schön, 2007].

Mechanisms of action. *Imiquimod and Toll-like receptors*. Imiquimod is a Toll-like receptor (TLR) 7 and 8 agonist. TLRs are a group of pattern recognition receptors (PRRs) that play a major role in innate immunity by identifying conserved pathogen-associated molecular patterns (PAMPs) of microorganisms, and inducing and cytokine production [Kobold, 2014, Wang, 2014]. TLR7 and 8 are predominantly expressed intracellurarly on the endosomal membranes and are restricted to several types of immune cells, including plasmocytoid dendritic cells (pDC). The natural ligand of TLR7 and 8 are single-stranded RNAs of invading microorganismis, specifically viruses [Schön, 2008, Kobold, 2014]. Upon activation of TLR7 pDC mature towards antigen presenting cells (APC) or to cytotoxic dendritic cells that directly kill tumor cells. In response to the activation of TLR7 and 8 nuclear factor - kappa B (NF-kB) is released. NF-kB induces production of several pro-inflammatory cytokines, including IL-2, IL-6, IL-8, IL-12, IL-18 and INF-α. Secretion of IL-12, IL-18 and INF-α stimulates production of INF-γ by naïve T cells, thus resulting in a Th1 mediated immune response [Cantisani, 2012]. Activation of NK cells and increased lysis of NK-dependent targets is also observed [Kobold, 2014]. Imiquimod above all is believed to induce apoptosis. Increased expression of the so called death receptor CD95 (Fas) has been noted *in vivo* on basal cell carcinoma (BCC) cells together with decreased expression of anti-apoptotic protein BCL-2 [Schön, 2007]. Increased angiogenesis is characteristic feature of the BCC and to a lesser extent in actinic keratosis (AKs) and warts [Newell, 2003]. Imiquimod has demonstrated anti-angiogenic properties by inducing production of interferons-α and γ, IL-10 and IL-12. Interferons decrease production of pro-angiogenic factors, including FGFb, IL-8, urokinase plasminogen activator, MMP-1 and induce endothelial apoptosis. IL-10 inhibits endothelial proliferation

and migration by reducing VEGF production [Vincent, 2005, Cantisani, 2012].

Imiquimod indications. Imiquimod 5% was authorized for topical use by the European Medicines Agency (EMA) in 1998 for the treatment of superficial BCCs, anogenital warts and AKs. Imiquimod 3,75% cream was authorised by the EMA in 2012 as a topical medicinal for the treatment of clinically typical actinic keratosis on the whole face and the balding scalp. In comparison to imiquimod 5%, imiquimod 3,75% has lower concentration that allows treatment of areas larger than 25 cm^2 and provides less adverse effects.

Actinic keratosis. AK is considered by many an intermediate skin lesion in the continuous progression of chronically photodamaged skin to squamous cell carcinoma (SCC) [Goldenberg, 2014]. AK is the most common pre-malignant lesion – up to 60% of individuals habitually exposed to UV radiation will develop at least one AK [Gordon, 2013]. Treatment of AK is advised since 25-60% of SCCs arise from AKs [Gordon, 2013].

AKs are lesions that develop in the cancerization field. The concept of field cancerization was first postulated by *Slaughter et al* in 1953 in the context of oral cancers and is defined as accumulation of genetically altered monoclonal cells in an area exposed to a carcinogen, e.g. UV radiation, cells do not demonstrate metastatic behavior or invasive growth. Histopathological examination of the biopsied tissue adherent to the actinic keratosis did not contain tumor cells, however genetic testing revealed mutations of the *p53* tumor suppresser gene [Braakhuis, 2003, Szeimies, 2012].

Lesion-directed therapy (LDT) of AKs includes cryotherapy, application of imiquimod 5%, laser therapy, curettage and dermabrasion. Imiquimod 5% is significantly more effective than the vehicle alone and leads to complete clearance of 50% of AKs [Hadley, 2006]. The outcome is comparable to diclofenac 3%. More data is needed to compare efficacy of 5% imiquimod to photodynamic therapy (PDT) and to 5-floururacil [Gupta, 2012]. Adverse effects included erythema, edema, induration, vesicles, erosion, ulceration, excoriation [Stockfleth, 2002]. Adverse effects are more prominent with imiquimod 5% in comparison to imiquimod 3,75% and has led to increased withdrawal of patients from trials [Gupta, 2012]. Unfotunately, LDT does not treat the cancerization field, thus recurrence of AK lesions is highly possible [Goldenberg, 2014].

Field-directed therapy (FDT) is aimed at treating not only visible AK lesions, but also surrounding subclinical lesions in the cancerization field. FDT includes imiquimod 3,75%, PDT and ingenolmebutate [Goldenberg, 2014]. The immune response to imiquimodincreases the amount of clinically visible lesions during treatment, this can only be achived

byimiquimod 3,75%. Therefore, a new efficacy assessment method was developed known as Lmax. This method evaluates the maximum lesion count during the treatment and compares it to the final lesion count. Two 14 week, placebo-controlled, double blind studies demonstrated an increase of median lesion count from 10 to 22 lesions during treatment. During the final follow-up a statistically significant decrease in median percentage of the lesion count was 81.8% from the baseline compared to 92.2% from Lmax [Stockfleth, 2014].

Basal cell carcinoma (BCC). BCCs make up 80% off all skin cancers. Several treatment options are available for low-risk superficial and nodular BCCs, including PDT, imiquimod 5%, 5-fluoruracil (5-FU), cryosurgery and excisional surgery as the gold standard. In a randomized study superficial BCCs were treated with imiquimod 5% for 6 weeks and nodular BCCs for 12 weeks, another group of patients was treated surgically. In a follop-up visit after 3 years complete clearence with no reccurence was notted in 83% in the imiquimod group, in comparison to 98% in the surgical excission group. Authors inisist that imiquimod is inferior to excissional surgery, however it still remains an effective option in low-risk superficial, small size BCCs, in delicate anatomical sites, as well as in cases where patients refuse surgical treatment [Bath-Hextall, 2014]. Imiquimod is found to be superior to PDT and 5-FU in the treatment of low-risk superficial BCCs [Arits, 2013]. Imiquimod is also considered more cost effective than PDT and surgery in treatment of BCCs [Aguilar, 2010].

Anogenital warts also known as condylomaaccuminatum (CA) are caused by HPV types 6 and 11. Imiquimod has shown variable results in complete clearance of CA ranging from 35-68%. Treatment continues for maximum of 16 weeks and adverse local reactions decrease patient adherence. Recurrence rates are relatively low 6-26%. In comparison, cryotherapy achieves 44-75% clearance rates and 21-42% recurrence rates [Lacey, 2012].

Imiquimod vs. resiquimod. Resiquimod is a more potent and soluble TLR7 and 8 agonist thanimiquimod that producesproduces a 50- to 100-fold cytokine response [**Wu, 2004**, **Meyer, 2013**]. Resiquimodtrialed for treatment of anogenital herpes lesions, due to the stimulation of antigen specific immunity mediated throug Th1 cells and a possible ability to decrease HSV shedding. Recent publications show that resiquimod does not decrease recurrence rates of HSV infection, in addition adverse effects at the application site such as prolonged healing time of herpes lesions, erythema, erosions and ulceration hinder the tolerability of the drug [**Wu, 2004, Mark, 2014**]. Resiquimod was also used as an adjuvant for HPV vaccines *in vivo*. The results are inssuficient and further investigation is needed [Sajadian, 2014].

Off-label imiquimod use. Due to the ability of imiquimod to rapidly and potently stimulate both innate and adaptive arms of the immune system, imiquimod has rapidly been recognized as a potential candidate for off-label use in over 60 conditions as presented in numerous case reports, letters and small trials. These conditions included SCC, cutaneous T-cell lymphoma, Merkel cell carcinoma, Kaposi sarcoma and oral lichen planus [**Cantisani**, 2012, **Ganijan, 2009**]. Most of the clinical cases reported complete clearance with no evidence of reoccurance. Overall, it is thought that there is a definite therapeuticalpotencial of imiquimod for these diseases. Keloids are a common manifestation of the woundhealing process after trauma to the skin. Topical application of imquimod 5% significantly decreases keloid recurrence after shave biopsy [**Berman**, 2009]. Unfortunately, there was no efficacy of imiquimod 5% for the treatment of molluscumconatagiosum in 2-12 years old pediatric patients, thus cryotherapy remains a main stay treatment **[Katz, 2014].** The majority of studies showed that topical imiquimod 5% application under occlusion is an effective and safe treatment option for of cutaneous melanoma metastases. Even if this treatment doesn't stop the disease progression, it is useful in clearing cutaneous metastases spreading from melanoma primary tumor **[Sisti, 2014].**

Combination therapy with imiquimod. There is a vast amount of studies and case reports describing possible combination therapies using imiquimod due to its immunomodulatory properties and synergistic affects.

Immunocryotherapy is a combined cryosurgical treatment with topical application of imiquimod. It has been proposed to improve treatment efficacy due to the synergistic affects, while increasing tolerability and patient adherence. There are several reports on successful management of nodular BCCs, SCCs and AKs with immunocryotherapy **[MacFarlane, 2011].**

Successful combination of imiquimod and PDT was described in treatment ofextramammary Paget's disease **[Jing, 2014].**

Low-fluence fractional lasers are being assessed to increase cutaneous drug permeation of imiquimod to decrease application doses and thus achieve lesser adverse event rates **[Lee, 2011]** Imiquimod 5% cream has been successfully used in pretreatment of Moh's micrographic surgery for primary nodular BCCs, decreasing the size of the tumor and of the surgical defect **[van der Geer, 2012].**

These findings suggest that imiquimod in combination with other therapeutic methods may improve the therapeutic efficacy of many dermatological conditions, reduce the necessity for surgical procedures and increase the cosmetic outcome and the lesion clearance rate.

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CHRONIC TONSILLITIS AND SKIN DISEASES

Asoc.prof.Ligija Kise, Asoc.prof.Janis Kisis
Riga Stradins University

Group A streptococcal upper respiratory infections are well known to be precusours of a number of disease processes. Some inflammatory skin diseases are known to be related to tonsil focal infection. Psoriasis is a common skin disease with strong genetic associations and environmental trigger. Psoriatic lesions are caused by abnormal reactivity of specific Tly in the skin. T cells from patients with psoriasis show increased responses to homologous peptides from streptococcal M proteins and human epidermal keratins. The palatine tonsils might play a major role in psoriasis as they are common site for streptococcal infections and could lead to the initiation and exacerbation of psoriasis. Hyperresponses against alfa-streptococci are seen also from palmar pustulosis patients. Silent and chronic focal infections in the tonsils could cause chronic skin diseases and tonsillectomy is often efficient in those cases. A tonsillectomy leads to the reduction of serum levels of IL-8 and IL-6, as tonsillar T cells with alfa-streptococcal antigen enhanced production of IL-6, INF-gamma, TNF-alfa and expression of cutaneous lymphocyte associated antigen, a homing receptor related to migration into the skin and transforming growth factor-beta production. Tonsillectomy rapidly improve the skin lesions.

КОМБИНИРОВАННАЯ ТЕРАПИЯ «ПУВА + ИНТЕРФЕРОН-А» У ПАЦИЕНТОВ С Т-КЛЕТОЧНЫМИ ЛИМФОМАМИ КОЖИ

Е.М. Анпилогова, О.Ю. Олисова, К.В. Смирнов, Н.Г.Чернова
ГБОУ ВПО Первый МГМУ им. И.М. Сеченова Минздрава России

Введение. Т-клеточные лимфомы кожи (ТКЛК) представляют собой гетерогенную группу неопластических заболеваний, обусловленных пролиферациеий клона лимфоцитов в коже и составляют более 65% первичных лимфом кожи. На долю лимфом кожи приходится 2% от всех дерматологических заболеваний. В последнее время зафиксирован заметный рост заболеваемости