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Research Article

Early Interruption of ongoing Posttraumatic Dystrophy

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Abstract: Posttraumatic dystrophy remains an unresolved therapeutical problem. The innate immunity response persists with local perpetuation of vicious circles of aseptic inflammatory reactions. Representative cells for such reactions are the lymphocytes and especially the ubiquitous tissue homing natural killing T cells NKT. Lymphotoxic drugs (glucocorticoides GC) showed the expected good effect in 9 patients (preliminary report).

Keywords: DAMPs; dNKT Cells; Glucocorticoid; Innate Immunity; Lymphotoxic Drug; Posttraumatic Dystrophy

Introduction

Posttraumatic dystrophy remains an unresolved therapeutic problem. Recently the origin of this complication was deduced on damage associated molecular patterns DAMPs, which are formed during tissue trauma from cellular fragments and humoral processes. From the beginning the innate immunity reacts on these "foreign" self molecules with activation of cells and cytokines. Phagocytosis by antigen presenting cells APC provides a strong control of detritus to detect invaders and prevent dangers for the host (Figure 1). Normally posttraumatic inflammatory reaction is aseptic and healing is reached in two to three weeks. In this period the detritus should be absorbed and the local homeostasis restored. Any disorder like hypoxia provokes the activation of local transient receptor potentials, acidosis by free radicals and cellular response. The innate immunity response persists with local perpetuation of vicious circles of aseptic inflammatory reactions. Representative cells for such reactions are the lymphocytes and especially the ubiquitous tissue homing natural killing T cells NKT.- Owing their plasticity in different tissues they imply divers T cell receptors and are therefore named dNKT cells. They are self propagating and stimulate the building of neutrophils and B-cells beside extrusion of cytokine storm (Table 1).

Taking together the conclusion is to use lymphotoxic drugs to suppress lymphocytes in case of prolonged posttraumatic aseptic inflammatory reaction with clinical signs and symptoms locally around the trauma region.

Materials and Methods

For the first time nine consecutive out-patients with traumata of upper extremity or foot were treated because of persistent pain and restricted functionality of the traumatized extremity. Further details are provided in Table 3, the reader is requested to see there. As usual, venous oxygen pressure was high on the affected limb and lower on contralateral side [2,3]. Referring therapy there are several international communications [4,5], which recommend the use of GC generally in the case of perpetual inflammatory reactions. Different diagnoses from distinct clinical departments make it difficult to transfer this recommendation to Posttraumatic Dystrophy where damage of tissues triggers the inflammation. It is notable that most patients were affected by healthy conditions. Furthermore the aseptic posttraumatic inflammatory reactions are locally developed and maintained by innate immunity. Therefore the effectors of dNKT cells (Table 1) [6] were compared with the specific efficacy of GC analyzed in three pharmacological publications [7-10] (Table 2A and Table 2B). Nearly all cytokines and chemokines of dNKT effectors were blocked also the transcription factor iNOS, cellular immune response, T cell development and antigene presentation. Further transcription factors of the cytosolic pathway are suppressed and prevent the transcription of proinflammatory cytokines [10]. These results encouraged to use GC in posttraumatic patients with chronification of innate inflammatory reactions and typical PTD history (8 to 13 weeks of aggravation), clinical signs and symptoms (Table 3).

age (yr)	m/fm	trauma diagnosis	PTD diagnosis after (wk)	therapy with proved diagnosis PTD	outcome 3 wk after therapy
HAND (n = 7)					
59	m	humerus fx left	12	glucocorticoid (GC) following circadian cycle of cortisol, schema see text physiotherapy, ergo therapy impulse compression cuff during therapy free periodes	wrist free function, shoulder slightly limited
72	fm	dist. radius fx left	9		free function
59	m	incision of carpal tunnel left	10		free function
62	fm	dist. radius fx left	8		free function
70	m	avulsion of hamulus ossis hamati left	12		improved hand function, wrist limited motion
82	fm	dist. forearm fx right	8		wrist free, arthrosis of carpal art. sellaris
64	m	dist. radius fx right	9		free function
FOOT (n = 2)					
18	m	metatarsal fx left	11	ditto	free function
60	fm	tarsal fx left	13		free function

Table 3: Patients: Nine consecutive patients with prolonged aseptic inflammatory reactions after traumatic incidence of the arm or foot were treated in the trauma department of affiliated Hospital of Medical School of University of Ulm in Immenstadt/Allgäu, Bavaria, Germany, leader Dr. A. Scola.

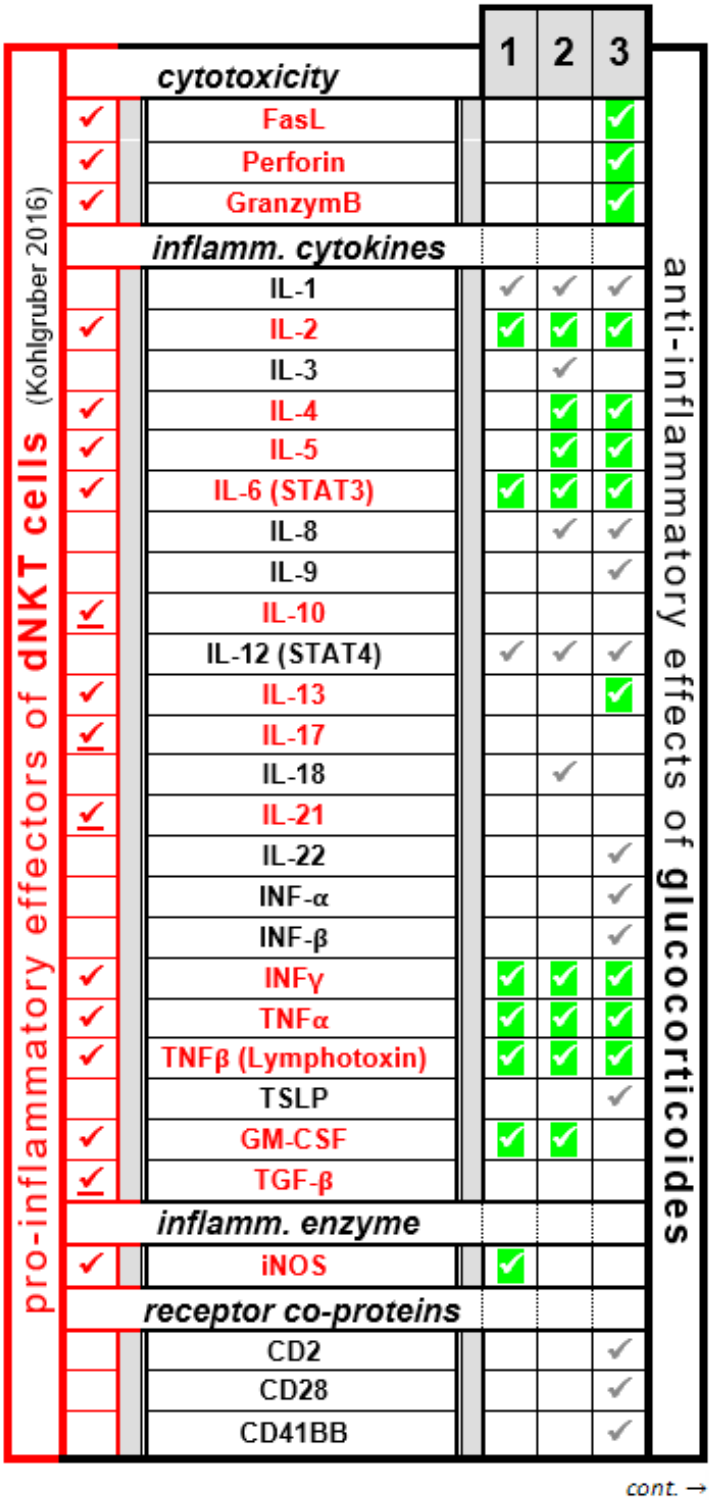

pro-inflammatory effectors of dNKT cells (Kohlgruber 2016)
anti-inflammatory effects of glucocorticoides
1
2
3
cytotoxicity
FasL
Perforin
GranzymB
inflamm. cytokines
IL-1
IL-2
IL-3
IL-4
IL-5
IL-6 (STAT3)
IL-8
IL-9
IL-10
IL-12 (STAT4)
IL-13
IL-17
IL-18
IL-21
IL-22
INF-α
INF-β
INFγ
TNFα
TNFβ (Lymphotoxin)
TSLP
GM-CSF
TGF-β
inflamm. enzyme
iNOS
receptor co-proteins
CD2
CD28
CD41BB
cont. →

Table 2A

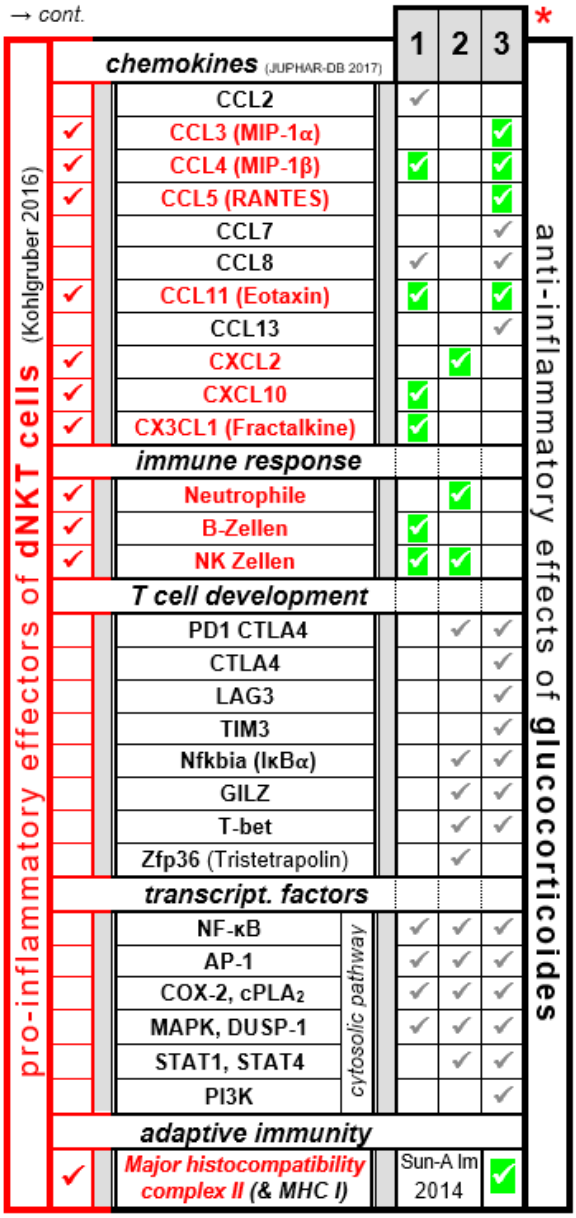
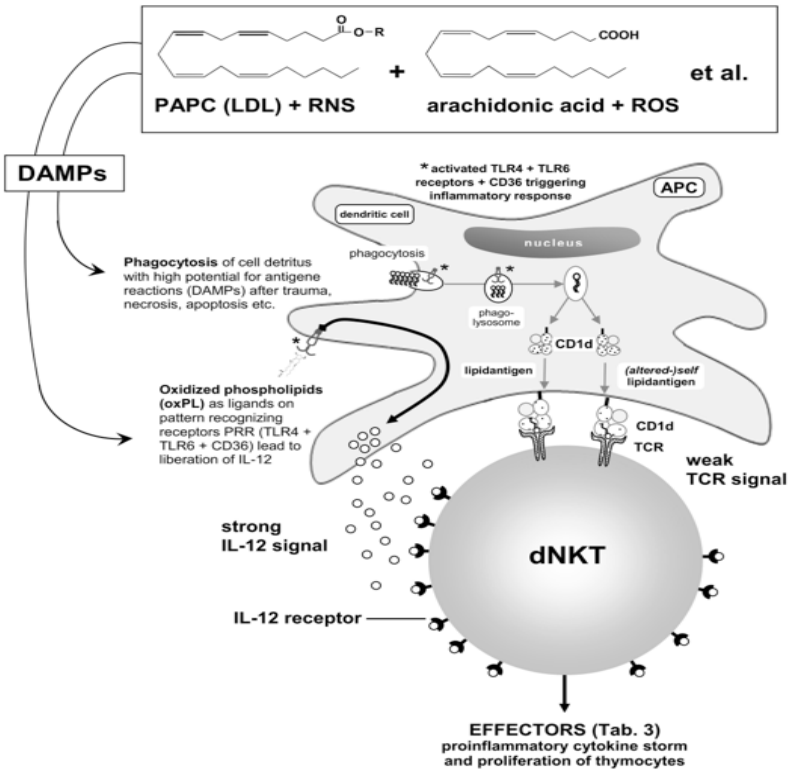


Table 2B

Table 2A and 2B: Comparison of activated dNKT cell effectors (red column, signs and terms,[6]) and their suppression by glucocorticoides (black column, signs and terms) with three pharmacologic articles 1: Czock 2005 [9], 2: Shimba 2020 [7,8], 3: Taves 2021 [10]. The majority of the activated dNKT cell effectors (25/29) are inhibited, only four cytokines out of 23 (indicated as **ü**: IL-10, IL-17, IL-21 and TGFβ) are not suppressed directly but indirectly reduced by impaired production of T helper cells. Coincidences are indicated as **ü**.. However, the activity of GC encompasses a large range of additional proinflammatory effectors (examples indicated as **ü**).



(**Abrivation:** PAPC 1-palmitoyl-2-arachidonyl-sn-glycero-3-phosphatidylcholine, LDL low density lipoprotein, RNS reactive nitrogen species, ROS reactive oxygen species, TLR toll-like receptor, CD cluster of differentiation)

Figure 1: (mod. based on [11] **):** Schematic presentation of activation of dNKT cell through antigene presenting dendritic cell activated T cell receptor (weak) and strong IL receptor signal (IL-12, extruded form DC granules). Effectors see Table 3.

		EFFECTORS of activated dNKT cell
Pro-inflammatory	cytokines	IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9,
		(IL-10), IL-12, IL-13, (IL-17), IL-18, IL-21, IL-22, INF-α, INF-β, INF-γ, TNFα, TNFβ (lymphotoxin), TSLP, GM-CSF, TGF-β
	chemokines	CCL2, CCL3 (MIP-1α), CCL4 (MIP-1β), CCL5 (RANTES), CCL7, CCL8, CCL11 (Eotaxin), CCL13, CXCL5, CXCL10, CX3CL1 (fractalkine)
	enzyme	iNOS
cytotoxicity		Fas-Ligand, Perforin, Granzyme B
receptor co-proteins		CD2, CD28, CD41BB
enhanced immune responses		neutrophils, eosinophils, T cells, B cells, NK cells, T_H1 cells, macrophages M1, DC
T cell development		PD-1, CTLA4, LAG-3, TIM3, Nfkbia (IκBα),
		GILZ, T-bet, Zfp36 (tristetrapolin);
		cell-communication: Cx 32

enhanced Adaptive Immunity	MHC I, MHC II
transcription factors	NF-κB, AP-1, COX-2, $cPLA_2$, MAPK,
(cytosolic pathway)	DUSP-1, STAT1, STAT4, PI3K

Table 1: Effectors of activated dNKT cell (cytokine storm) (6). Exocytosis starts about 30 min after activation due to innate microRNA of cytokins (INF-γ, IL-4) and lasts up to 2 days.

Treatment (consider contraindications) [9] The treatment with glucocorticoides (GC) was initiated with 80 mg a day for 4 days (à three doses each day in 8 hrs interval: 40 / 20 / 20 mg, following the circadian cycle of cortisol), 4 days à 40 mg (8 hrs interval 20 / 10 / 10 mg) and 4 days á 20 mg (8 hrs interval 10 / 5 / 5 mg). If necessary an extension of the therapy is possible even with higher doses.

Results

As expected the signs of aseptic inflammation disappeared in one to two days and the efficiency of physiotherapy increased. Never the less the glucocorticoid therapy was completed according to the scheme. With normal clinical findings after accomplished therapy the venous oxygen measurement was not controlled. No rebound phenomenon was observed.

Discussion

Enormous progress in immunology, namely aseptic inflammatory reactions after traumata by DAMPs [1] changed the point of view for effective treatment fundamentally. With PTD treatment common antiphlogistic drugs had no effects for too small specivity of action. In contrast the effectors of NKT cells are suppressed and blocked for a great amount with application of GC. The first indication of GC in PTD showed good clinical results. As prelimitary report further experience in this field is needed.

Conclusion

The insight into the nature of interplay between PAMPs and innate immunity allows a better understanding of aseptic inflammation after traumatic tissue lesions. The question about normal and atypical development becomes clearer answered actually. Cellular and humoral factors can work together in order to support the host in healing intentions. But sometimes gets the innate immunity irritated by molecules which were built by the host and provoke a long lasting inflammatory reaction. This bears the danger of creating antigens against host tissues, which leads to a disaster like PTD [12]. Therefore the necessity exists to battle against this complication as soon as possible. GC repress the lymphocytes and their effectors. First applications against immanent posttraumatic dystrophy showed very good results.

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Ethical Guidelines: Not applicable

Conflict of interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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