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Complex pharmaceutical Traumeel® S (Tr14) improves the resolution of inflammation

Paul M. Jordan and Oliver Werz

Abstract: The resolution of inflammation has to date been explained by the disappearance of inflammatory messenger substances, the production of which is suppressed by non-steroidal anti-inflammatory drugs (NSAIDs). The latest studies, however, show that the resolution of inflammation is an actively controlled process, involving specialised pro-resolving mediators. Their formation is promoted by the complex pharmaceutical preparation Tr14 (Traumeel® S).

The resolution of inflammation is an actively controlled process

Virtually all injuries and tissue damage are associated with inflammation, which, as part of the healing process, helps to repair damaged tissue and reinstate homoeostasis. Insufficient resolution of inflammation increases the risk of a persistent "silent" inflammation, which may lead to chronic pain, persistent tissue damage and fibrosis [1]. Targeted promotion of the resolution of inflammation can reduce said risks, alleviate pain and improve healing.

For a long time, it was assumed that the inflammatory mediators derived from arachidonic acid (eicosanoids, such as thromboxanes, prostaglandins and leukotrienes) were decisive for maintaining the inflammatory process. This conception also influenced the pharmacological interventions, based on the assumption that inflammation ends once the trigger is no longer present or mediators are no longer produced. In clinical practice, however, persistent inflammations occurred in spite of medication, which was difficult to explain using the model mentioned. Consequently, fundamental research examined the entire inflammatory process and its pharmacological modulation more closely. Thus, scientists discovered, for example, that glucocorticoids, despite having an immunosuppressive effect, interfere with wound healing, while NSAIDs, such as coxibs, increase the risk of arterial ischaemia. It was, moreover, revealed that the resolution of inflammation is not a passive process, merely characterised by the absence of inflammatory mediator formation, but an actively controlled process involving specialised cells and specific mediators which promote resolution [1].

The multi-component pharmaceutical Tr14 (Traumeel® S) has a positive effect on illnesses caused by an underlying inflammatory process. Besides observational studies, randomised clinical trials comparing Tr14 with NSAIDs or a placebo also demonstrated its fundamental efficacy and good tolerance [2, 3]. Against the background of the latest findings on the resolution of the inflammatory process, further pre-clinical investigations have now been conducted in order to understand whether, and, if applicable, how, Tr14 influences the resolution of inflammation at the cellular and molecular levels [3].

Formation of specialised pro-resolving mediators as a new target

During early stages of inflammation, in particular pro-inflammatory cytokines are generated, which stimulate the formation of macrophages of the M1 phenotype, which are involved in the production of pro-inflammatory lipid mediators (LMs) (**Fig. 1**). The pro-inflammatory LMs comprise leukotrienes (LTs) and prostaglandins (PGs), which are formed from arachidonic acid (AA) through the initial effect of the key enzymes 5-lipoxygenase (5-LOX) and/or cyclooxygenases (COX-1 and COX-2). NSAIDs block the biosynthesis of PGs, thereby suppressing the most important signs of inflammation. During the resolution phase, a change in the macrophages occurs: Pro-inflammatory M1 macrophages change their phenotype and become resolution-promoting M2 macrophages, which simultaneously produce so-called specialised pro-resolving mediators (SPMs). The resolution-promoting SPMs include lipoxins (LXs), resolvins (Rvs), maresins (MaRs) and protectins (PDs), which, are formed, along with the 5-LOX, with the aid of further lipoxygenases, namely 12-/15-LOX, from arachidonic acid,

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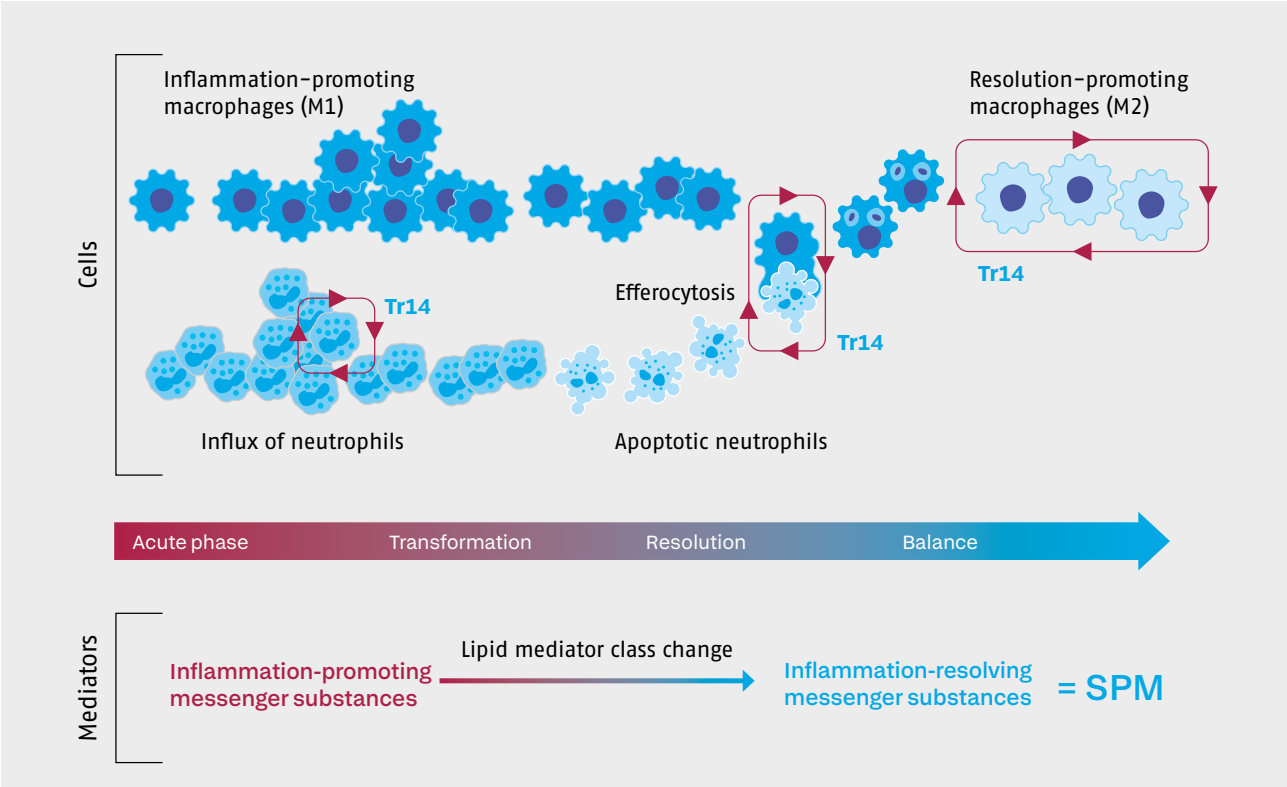

Fig. 1. Schematic representation of some key elements of the inflammatory process: During the early stages of inflammation, inflammation-promoting messenger substances, neutrophilic granulocytes and M1 macrophages prevail. Over the course of time, phagocytosis of the neutrophils by macrophages (efferocytosis), as well as predominance of resolution-promoting M2 macrophages occurs. At the level of the mediators, a shift in the lipid mediator class occurs, leading to the predominance of specialised pro-resolving mediators (SPMs) in subsequent phases [©Heel].

eicosapentaenoic acid and docosahexaenoic acid. These SPMs act upon G protein-coupled receptors on various immune cells, and bring about the adequate resolution of the inflammation, for instance by limiting excessive infiltration of neutrophils. Furthermore, they reduce the formation of pro-inflammatory cytokines and stimulate phagocytosis and/or efferocytosis of apoptotic cells. From a pharmacological perspective, it therefore appears obvious to promote the resolution of an inflammation, for example by way of targeted stimulation of endogenous SPM production, as has already been observed after using natural products. A pre-clinical study showed that Tr14 can likewise exert this resolution-promoting effect [3]. Tr14 contains 14 plant-based and mineral ingredients, which were obtained in line with the regulations of the European Pharmacopoeia (Ph. Eur.). The raw materials of the 12 plant-based components are fresh plants, the content of which adds up to 232 µg/ml in the pharmaceutical preparation Tr14 [3].

Neutrophil infiltration in vivo reduced significantly

For in vivo experiments, a validated inflammatory mouse model was used, which involved a peritonitis being induced through intra-peritoneal (i.p.) administration of zymosan. The mice were given either a low dose (1.5 ml/kg) or a high dose (3 ml/kg) of Tr14, or 0.9% saline solution for comparison, daily over six days prior to the zymosan injection (prophylactic administration) or at four and eight hours afterward (therapeutic administration). The maximum cell infiltration was reached four hours after the zymosan injection (i.p.). The infiltrate predominantly contained neutrophils (PMNs), the number of which was significantly reduced ($p < 0.01$) through the prophylactic administration of the lower dose of Tr14 after eight hours. In the investigation, Tr14 shortened the resolution interval R_i (= time interval between the point in time T_{max}, at which the highest PMN number was measured, and the point in time T_{50}, at which the PMN number had dropped to half of the maximum value) with the higher dose by 1.3, and, with the lower dose, by 5.9 hours (**Fig. 2**) [3]. Interestingly, the higher dose of Tr14 increased the number of macrophages involved in the efferocytosis significantly after four hours ($p < 0.05$), which was not the case with the lower dose or at later points in time (**Fig. 2**).

Change of class from pro-inflammatory to pro-resolving lipid mediators

In comparison to the control group, therapeutic administration of Tr14 significantly increased the production of resolvins during both the early (after 24 hours; $p < 0.05$) and the late (after 15 days; $p < 0.01$) resolution phase of the inflammation (**Fig. 3**). Although the prophylactic treatment with Tr14 did not significantly influence the overall production of LMs, it did increase the ratio of SPMs (PD1, MaR1, RvD2, RvD5 and LXA_4) over LMs formed by COX (PGE_2 and TXB_2), which indicates that Tr14 promotes a lipid mediator class change from pro-inflammatory to pro-resolving LMs (**Fig. 4**).

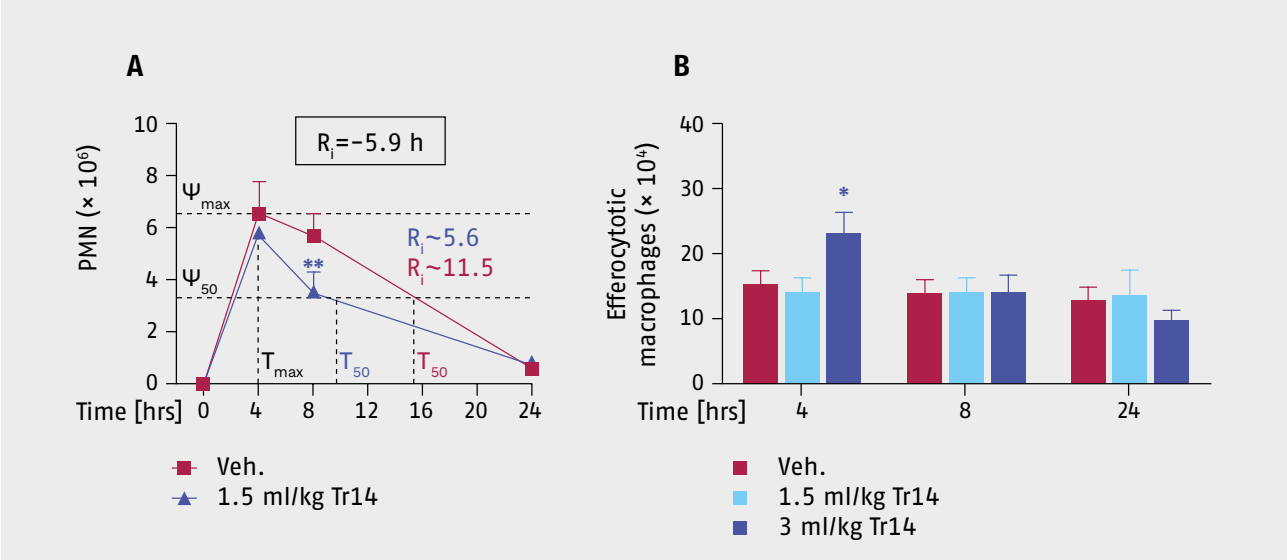

Fig. 2. Prophylactic administration of Tr14 in zymosan-induced peritonitis:
(A) Shortened resolution interval: Representation of the number of neutrophils in the exudate as a function of time. In comparison to the vehicle (Veh.), Tr14 (1.5 ml/kg) reduced the number of neutrophils (PMN) significantly after 8 hours and shortened the resolution interval (R_i) of the inflammation by 5.9 hours. (B) Increased efferocytosis: Representation of the number of macrophages as a function of time. In comparison to the vehicle, the higher dose of Tr14 (3 ml/kg) significantly increased the number of macrophages involved in the efferocytosis after 4 hours [3]. * p < 0,05; ** p < 0,01

Tr14 shifts the lipid mediator profile during the macrophage polarisation

The ability of Tr14 to influence the polarisation of macrophages to the M1 and M2 macrophage types was investigated in vitro. To this aim, macrophages were treated with either a low (0.1%) or high (10%) dose of Tr14 and polarised for 48 hours, either to M1 macrophages with LPS/IFN-γ or to M2 macrophages using IL-4. These macrophages were then incubated with *Staphylococcus aureus*, and the LMs formed were analysed. Here, in particular the polarised M2 macrophages exhibited an increased formation of 15-LOX-1-mediated LMs, especially SPMs. In contrast, Tr14 reduced the proportion of 5-LOX-mediated LTB_4 and COX-mediated PGE_2, indicating that Tr14 shifts the LM formation during macrophage polarisation towards a resolution-promoting LM profile [3].

Effects at the molecular level explain the differing (side) effect profile

The results of the study show that Tr14 promotes the resolution of inflammation. It was shown that Tr14 shortens the resolution interval and increases the efferocytosis capacity

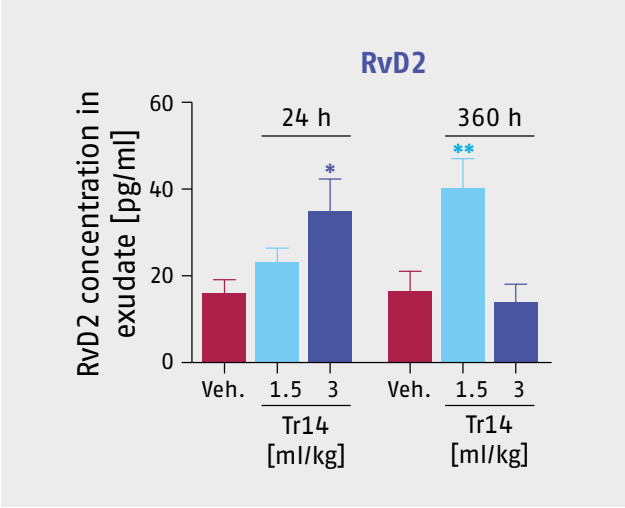

Fig. 3. Increased production of resolution-promoting lipid mediators.
In comparison to the control group with vehicle (Veh.), therapeutic administration of Tr14 significantly increased the production of resolvins (in this case: RvD2) during both the early (after 24 hours) and late (after 15 days) resolution phase of inflammation (* p < 0,05; ** p < 0,01) [3].

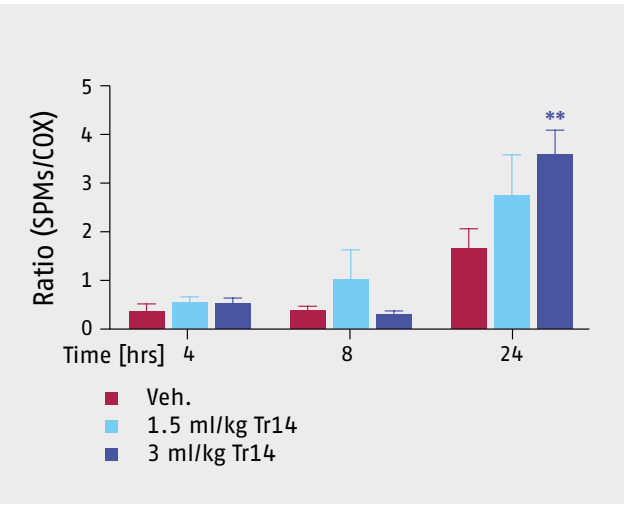

Fig. 4. Increased ratio of resolution-promoting lipid mediators in comparison to COX products.
Compared to the control group with vehicle, Tr14 significantly increased the ratio of resolution-promoting mediators (SPMs) over COX-associated, inflammation-promoting mediators (PGE_2 and TXB_2) 24 hours after prophylactic administration (** p < 0,01) [3].

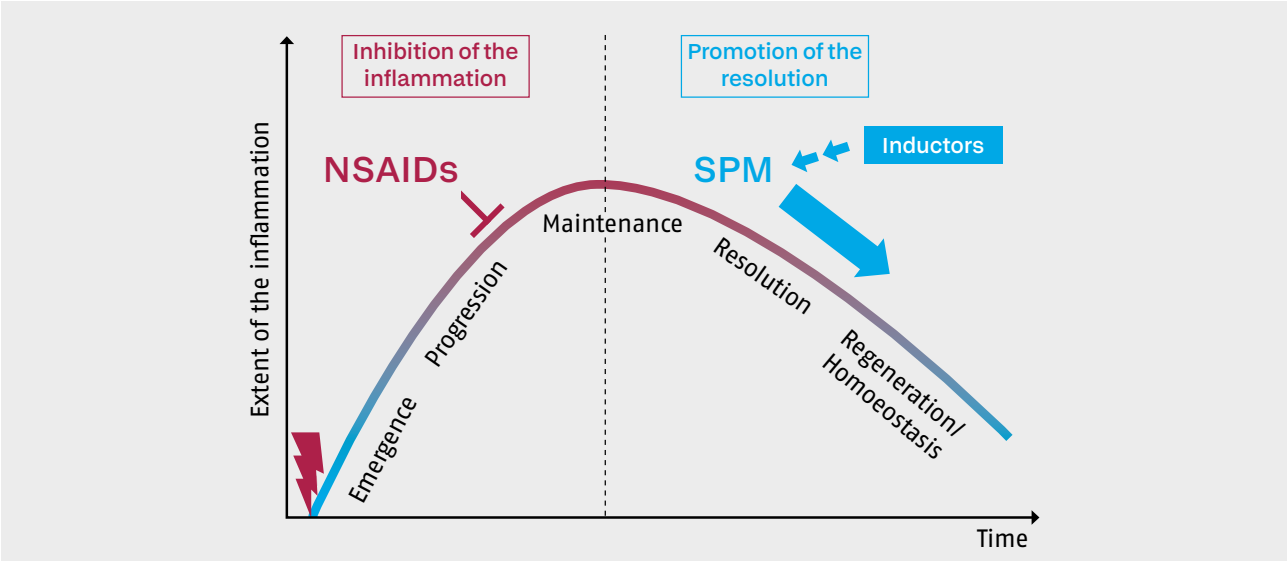

Fig. 5. Schematic progression of a musculoskeletal inflammation and the influence of NSAIDs and SPMs on its course. Besides the inhibition of inflammation, the promotion of resolution will increasingly form the focus of attention in future research. (Modified according to [4])

of macrophages. At the level of the messenger substances, no reduction of pro-inflammatory mediators, such as PGs and LTs, can be seen, but rather an increase in the resolution-promoting mediators, such as resolvins, thus also resulting in a change in the ratio of SPMs to COX products. Accordingly, Tr14 also does not bring about the gastrointestinal and cardiovascular side effects that are typical of NSAIDs, which primarily result from COX inhibition. Instead of inhibiting the inflammation, Tr14 promotes the resolution process (**Fig. 5**), which is reflected in shortened resolution intervals and an increased number of efferocytotic macrophages. These macrophages play a crucial role in eliminating apoptotic PMNs and cellular debris produced at the onset of inflammation. The results of the present in-vitro/in-vivo study thus make for an interesting contribution towards explaining the mode of action of Tr14, supporting numerous clinical reports on its analgesic effect.

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