УДК 615.276.015.32.036.8

AN INTEGRATIVE REVIEW OF THE EVIDENCE ON THE EFFICACY OF THE ANTIHOMOTOXIC MEDICATION TRAUMEEL

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Introduction. *Traumeel is a homeopathic medication used for the stand-alone or adjuvant bioregulatory therapy of inflammatory diseases of different organs and tissues, including locomotor diseases (tendovaginitis, bursitis, styloiditis, periarthritis, etc.) and various posttraumatic conditions (postoperative soft tissue swelling, muscle strain, and ligament sprain).*

Objective: *to review the scientific literature on the efficiency of using Traumeel to treat inflammatory diseases of different organs and tissues.*

Material and methods. *The available data on Traumeel were analyzed using an integrative approach, i.e. mixed methods. The analysis included both the determination of the level of evidence, by applying a hierarchical grading system, and the assessment of the data by non-hierarchical methods.*

Results. *Twenty-two works, including 3 reviews, 6 clinical trials, 7 prospective cohort studies, and 7 publications on the results of basic research studies were analyzed.*

Conclusion. *Studies on Traumeel comprise are a multifaceted and diverse evidence-base that increases every year. The integrative approach is of value in the context of individualized medical care.*

Key words: *bioregulatory therapy, locomotor diseases, posttraumatic conditions, integrative approach, evidence base.*

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INTRODUCTION

Traumeel is a homeopathic medicinal product that is applied according to bioregulatory principles derived from a homotoxicological approach and, therefore, also called antihomotoxic preparation. It is multicomponent and has been shown to have a multitarget action in the inflammatory immune network.

Traumeel is used for the adjuvant or stand-alone treatment of inflammatory diseases of different organs and tissues, including, in particular, of the musculoskeletal system (tendovaginitis, bursitis, styloiditis, epicondylitis, periarthritis, etc.), and post-traumatic conditions (post-operative swelling of soft tissues, strains, sprains).

The data for this review was obtained via a search of the literature using the search term "Traumeel" in the title and/or abstract and/or keywords of the article. In addition to this, available studies were requested from, and made available by, Biologische Heilmittel Heel.

The objective of this study was to obtain an overview of the evidence on the use of Traumeel for its main registered indication as stated above. Studies on a range of non-registered indications were excluded.

METHODS

This review applied an integrative, «mixed methods» approach with regard to the available data on Traumeel. This involved grading the level of evidence using one of the classical hierarchical evidence grading systems and complementing this by a non-hierarchical assessment of the available data.

For determining the level of evidence of each of the identified studies, the OCEBM 2011 Levels of Evidence schedule [1] for treatment benefits was used.

For the non-hierarchical evidence classification, the evidence mosaic categories as depicted in Figure 1 were used. In the «evidence mosaic» [2] approach, use is made of the metaphor that different research methods, each with their strengths and weaknesses, contribute to a «mosaic» of evidence.

Figure 1. Evidence Mosaic

RESULTS

Twenty-two studies were selected, including three review papers by C. Schneider [3], C. Müller-Löbnitz [4], and C. Speed [5]; six clinical trials by J. Zell [6, 7], W. Thiel [8, 9], D. Böhmer [10], S. Arora [11], C. González de Vega [12] and C. Lozada [13, 14]; seven prospective cohort studies by S. Zenner [15, 16], M. Weiser [17, 18], J. Ludwig [19], H. Birnesser [20] and C. Schneider [21, 22]; seven basic research studies by A. Conforti [23, 24], H. Enbergs [25], S. Lussignoli [26], H. Heine [27], S. Porozov [28], B. Seilheimer [29] and G.St. Laurent [30].

Four identified studies were not selected due to the absence of original research data [31–34].

The main characteristics of the included Traumeel studies as well as the evidence grading in accordance with the OCEBM Levels of Evidence Schedule are summarized in the Table.

The Table illustrates that treatment benefits of Traumeel are supported by the following levels of evidence: six clinical trials are graded as level-2 evidence; seven observational studies provide level-3 evidence, and seven basic research studies level-5 evidence. The three review papers reported in the Table were not graded as level-1 evidence because none of these reviews were systematic and, therefore, the criterion for level-1 evidence was not met.

The Table indicates that studies on topical, oral, and injectable modes of administration are available. The indications consist of acute sprains, strains and bruises; of soft-tissue rheumatic complaints such as epicondylitis, tendinitis, bursitis, etc.; and more chronic degenerative conditions such as osteoarthritis and rheumatoid arthritis. Broadly speaking, three types of indications can be distinguished: acute injuries, soft-tissue rheumatic complaints, and chronic degenerative rheumatic complaints.

Six trials provide level-2 evidence; four of these involve acute injuries (three acute sprains/contusions, one post-traumatic bloody effusion of the knee joint), one osteoarthritis of the knee, and one was a phase-1 clinical trial investigating the safety of orally administered Traumeel.

The trials by J. Zell [6, 7] and C. González de Vega [12] were for subjects with acute ankle sprains and involved both placebo (J. Zell) and active (C. González de Vega) controls. The placebo-controlled trial by D. Böhmer et al [10] included multiple sports injuries and, therefore, not exclusively subjects with ankle sprains. The trial by W. Thiel et al [8, 9] involved the treatment of post-traumatic bloody effusion of the knee joint and demonstrated objective differences in favor of Traumeel compared to placebo under strictly blinded conditions. The trial by C. Lozada et al [13, 14] demonstrated benefits of Traumeel in combination with Zeel compared to indistinguishable placebo in the treatment of osteoarthritis of the knee using a well validated outcome scale. The phase-1 trial by S. Arora [11] confirmed the safety of oral Traumeel in healthy subjects.

Seven observational cohort studies were identified that met the level-3 evidence criterion. Three of these studies were large, prospective cohort studies, which included all three types of indications. Two cohort studies included patients with acute sprains and contusions, and two studies included soft-tissue rheumatism (epicondylitis and tendinitis) patients. All these studies indicated that different modes of administration of Traumeel were effective and safe in daily practice.

Seven preclinical (4 *in vitro*, 3 *in vivo*) studies providing level-5 evidence were identified. The majority of these studies indicate that Traumeel may act as a multicomponent, multitarget immunomodulating drug. Various *in vitro* and *in vivo* studies confirm that Traumeel exerts an anti-inflammatory or rather «inflammation regulating» action without affecting the prostaglandin synthesis pathway, suggesting (and confirming the clinical data) that Traumeel can be a safe alternative to NSAIDs. One *in vitro* study on chondrocytes by B. Seilheimer et al [29] suggests that Traumeel inhibited metalloproteinases associated with pathological joint destruction. The *in vitro* ex-vivo study by H. Heine et al [27] suggests that Traumeel may play a role in re-establishing normal immune tolerance in rheumatoid arthritis patients. The innovative *in vivo* study by G. St. Laurent et al [30] which used high-throughput screening of the transcriptome, confirmed that Traumeel affected the gene expression of growth factor and other tissue generation pathways in the inflammatory cascade seen in a wound healing model.

In conclusion, there is broader level-2 evidence for the efficacy of Traumeel in acute sprains, and there is some level-2 evidence that Traumeel could be useful in the management of acute knee trauma as well as osteoarthritis of the knee. The evidence on the efficacy of Traumeel in acute sprains is further supported and confirmed by five cohort studies providing level-3 evidence for the same indication.

The evidence on the effectiveness of Traumeel in soft-tissue rheumatism is weaker and mainly supported by two comparative cohort studies providing level-3 evidence. There is a considerable amount of level-5 evidence which indicates that Traumeel acts as an «inflammation regulating» drug via various, including tissue regeneration, pathways.

The Traumeel evidence mosaic categories are visualized in Figure 2.

Figure 2 illustrates that the evidence base of Traumeel is supported by a broad mix of studies. Added value is provided by coherence between data from the different sources. For instance, the clinical trial data on the efficacy in acute ankle sprains is complemented by a large amount of observational data confirming that Traumeel is effective and safe in acute sprains.

It should be noted that three review papers referred to in the Table are included in the evidence mosaic. Whilst these studies did not meet the OCEBM criteria for level-1

Table

SUMMARY OF THE MAIN CHARACTERISTICS OF THE INCLUDED TRAUMEEL STUDIES AND EVIDENCE GRADING

Study design	First author (year)	Objective	OCEBM evidence level treatment benefits
Prospective cohort study	Zenner (1992) [16]	To assess the effectiveness and safety of Traumeel S injections as used in daily practice	3
Prospective cohort study	Zenner (1994) [15]	To assess the effectiveness and safety of Traumeel S ointment as used in daily practice	3
Prospective cohort study	Weiser (1996) [18] Zenner (reprint 1997) [17]	To assess the effectiveness and safety of Traumeel S drops and tablets in clinical practice	3
Prospective cohort study	Ludwig (2001) [19]	To assess the effectiveness and safety of Traumeel S ointment as used in children in daily practice	3
Prospective comparative cohort study	Birnesser (2004) [20]	To compare the effectiveness of Traumeel S injections with standard NSAID therapy in patients with epicondylitis	3
Prospective comparative cohort study	Schneider (2005) [22]	To compare the effectiveness of Traumeel ointment with diclofenac gel in patients with tendinopathies	3
Prospective comparative cohort study	Schneider (2008) [21]	To assess the effectiveness and safety of Traumeel compared with conventional therapies in the treatment of trauma and injuries	3
Randomized, placebo-controlled clinical trial	Zell (1988; original publication in German) [7] (1989 English translation of publication) [6]	Investigating the efficacy of Traumeel ointment in the treatment of ankle sprains	2
Randomized, placebo-controlled clinical trial	Thiel (1991; original publication in German) [9] (1994; English translation of publication) [8]	Investigating the efficacy of Traumeel intra-articular injections in the treatment of effusion of the knee joint	2
Randomized, placebo-controlled clinical trial	Böhmer (1992) [10]	Investigating the efficacy of Traumeel ointment in the treatment of various acute sport injuries	2
Phase-1 type clinical trial	Arora (2000) [11]	Investigating the safety of orally applied Traumeel in healthy volunteers	3
Randomized, active controlled clinical trial	González de Vega (full paper: 2013/ conference abstract 2012) [12, 35]	Comparing the efficacy of topical Traumeel with topical diclofenac gel in the management of acute ankle sprain	2
Randomized, double blind, placebo-controlled clinical trial	Lozada (2014, 2015) [13, 14] (abstracts)	Investigating the efficacy of intra-articular Traumeel and Zeel in patients with osteoarthritis of the knee	2
Review paper on Traumeel and its ingredients	Schneider (2011) [3]	Reviewing the role of Traumeel and its ingredients in the management of acute musculoskeletal injuries	n/a
Review paper on the clinical efficacy of Traumeel and its constituents	Müller-Löbnitz (2011) [4]	Reviewing the role of Traumeel and its constituents in registered indications	n/a
Review paper on the management of soft-tissue disorders and the role of Traumeel	Speed (2014) [5]	Review of challenges of pain management in soft-tissue disorders and the role of Traumeel as a multitarget therapy	n/a
Basic research, *in vitro* and *in vivo*	Conforti (1997) [24] Conforti (1998; German article including the data of the 1997 study) [23]	Testing the effect of Traumeel on superoxide anion production and human platelet adhesion	5
Basic research, *in vitro*	Enbergs (1998) [25]	Testing the effects of Traumeel on phagocyte and lymphocyte activity	5
Basic research, *in vivo*	Lussignoli (1999) [26]	Testing the effects of Traumeel on traumatic blood extravasation	5
Basic research, *in vitro* ex vivo	Heine (2002) [27]	Investigating the anti-inflammatory action of Traumeel	5
Basic research, *in vitro*	Porozov (2004) [28]	Investigating the effects of Traumeel S on resting and activated human T-cells, monocytes, and gut epithelial cells	5
Basic research, *in vitro*	Seilheimer (2009) [29]	Investigating the effects of Traumeel S on chondrocytes and human matrix metalloproteinases	5
Basic research, *in vivo*	St. Laurent (2013) [30]	Analysis of novel and therapeutically relevant changes in the transcriptome at several time points during wound healing	5

evidence, they are useful review papers that add something to the evidence mosaic. For instance, the review paper by C. Müller-Löbnitz [4] assesses the available data on Traumeel as well as its individual constituents. Whilst the latter does not provide direct evidence on Traumeel, it does provide some supportive evidence. Similarly, the review by C. Schneider et al [3] explores the literature on Traumeel and its ingredients with particular reference to the pathophysiology of inflammation. The review by C. Speed et al [5] focuses on soft-tissue disorders, including pathophysiology, and the challenges in the management of these conditions, including the possible role of Traumeel, are addressed. Therefore, by placing the available preclinical and clinical data in a pathophysiological as well as clinical context, this paper adds something to the evidence mosaic of Traumeel for these conditions.

The effects observed in the various preclinical investigations are fully consistent with the increasingly understood multiple pathways involved in the regulation of inflammation and other mechanisms involved in the healing processes following different types of trauma. The broad involvement of inflammation in many pathogenetic processes as well as the recovery from various acute traumas provides a logical backdrop for Traumeel's broad effectiveness, as observed in the variety of clinical studies available.

DISCUSSION

There is convincing evidence that Traumeel is effective in the treatment of acute sprains and emerging positive evidence in the clinical domains of osteoarthritis, rheumatoid arthritis, and knee trauma with effusion. Positive evidence is available for strain-related semi-chronic conditions, such as epicondylitis and tendinitis. Traumeel appears to act as a multicomponent drug via multiple pathways, making not only the mode of action, but also the relative safety compared to single-component, single-target drugs (such as NSAIDs) biologically plausible.

Whilst an extensive amount of scientific data has been obtained on Traumeel during the last 30 years, some weaknesses and areas of improvement in the evidence base should be mentioned. The evidence of Traumeel could be further strengthened by a systematic review of the trial data. For the three available trials on acute sprains/contusions, the conduction of a meta-analysis could be considered. The trial by D. Böhmer et al [10] included patients with multiple types of sports injuries (both contusions and sprains) of both upper and lower extremities, and this heterogeneity led to the Traumeel and placebo group not being fully comparable (59% of the Traumeel group had contusions versus 32% of the placebo group). The trial by C. Lozada et al [13, 14] involved treatment by Traumeel in combination with another homeopathic product; therefore, whilst this was a high-quality positive trial with a low risk of bias, the observed effects cannot be solely attributed to Traumeel. The *in vitro* investigation by H. Heine et al [27] is affected by a relatively small sample and the lack of proper controls; these results should therefore be interpreted with caution.

The available data on Traumeel suggest that there is a growing and multifaceted evidence base for this product. In our opinion, obtaining such an integrative, multifaceted perspective on the available evidence provides significant added value as a source for informing individualized patient care.

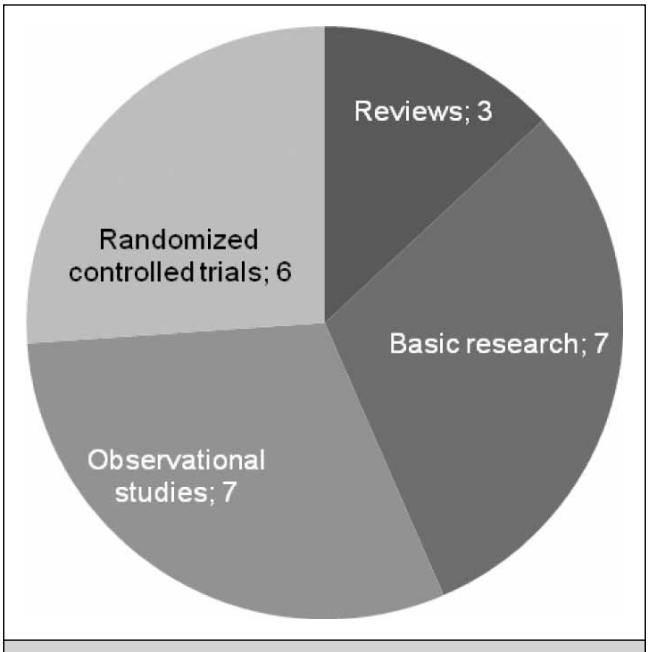

Figure 2. Traumeel Evidence Mosaic Chart

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Поступила 23 марта 2017 г.

ИНТЕГРАТИВНЫЙ ОБЗОР ДОКАЗАТЕЛЬСТВ ЭФФЕКТИВНОСТИ АНТИГОМОТОКСИЧНОГО ПРЕПАРАТА «ТРАУМЕЛЬ»

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РЕЗЮМЕ

Введение. Траумель представляет собой гомеопатическое лекарственное средство, применяемое в целях биорегуляционной терапии – основной или адъювантной – при воспалительных заболеваниях различных органов и тканей, включая заболевания опорно-двигательного аппарата (тендовагинит, бурсит, стилоидит, периартрит и т. д.), а также различные посттравматические состояния (послеоперационный отек мягких тканей, растяжение мышц и связок).

Цель исследования – обзор доказательных данных об эффективности применения препарата «Траумель» при воспалительных заболеваниях различных органов и тканей.

Материал и методы. Анализировались имеющиеся по препарату «Траумель» данные с использованием интегративного подхода, т.е. смешанными методами. Анализ включал как определение уровня доказательности данных с помощью иерархической системы оценки, так и оценку данных неиерархическими методами.

Результаты. Проанализировано 22 работы, включая 3 обзорных статьи, 6 клинических исследований, 7 проспективных когортных исследований, 7 публикаций по результатам фундаментальных исследований.

Заключение. Исследования по применению препарата «Траумель» составляют многогранную и разностороннюю доказательную базу, которая увеличивается с каждым годом. Использование интегративного подхода представляет ценность в контексте индивидуализированного медицинского обслуживания.

Ключевые слова: биорегуляционная терапия, заболевания опорно-двигательного аппарата, посттравматические состояния, интегративный подход, доказательная база.