Robbert van Haselen [1]

Integruota įrodymų apie antihomotoksinį vaistą *Traumeel* apžvalga

Tarptautinis integratyviosios medicinos institutas (INTMEDI), Kingstonas, Jungtinė Karalystė [1]

ĮŽANGA

***Traumeel* yra homeopatinis vaistinis preparatas, sukurtas laikantis homotoksikologinio požiūrio ir vartojamas remiantis bioreguliaciniais principais. Todėl taip pat vadinamas *antihomotoksiniu preparatu*. Tai daugiakomponentis preparatas, veikiantis daugelį uždegiminio imuninio tinklo taikinių.**

***Traumeel* vartojamas kaip adjuvantinis gydymas ar monoterapija gydyti įvairių organų ir audinių uždegimines ligas, ypač skeleto ir raumenų sistemos (tendovaginitą, bursitą, stiloiditą, epikondilitą, periartritą ir kt.), bei esant potrauminėms būklėms (pooperaciniam audinių patinimui, patempimui, pertempimui).**

Šią apžvalgą sudaro literatūros duomenys, kurių buvo ieškoma pagal terminą „*Traumeel*“ (pavadinime ir / arba santraukoje ir / arba tarp reikšminių žodžių). Be to, tyrimais pasidalijo ir kompanija „Biologische Heilmittel Heel“.

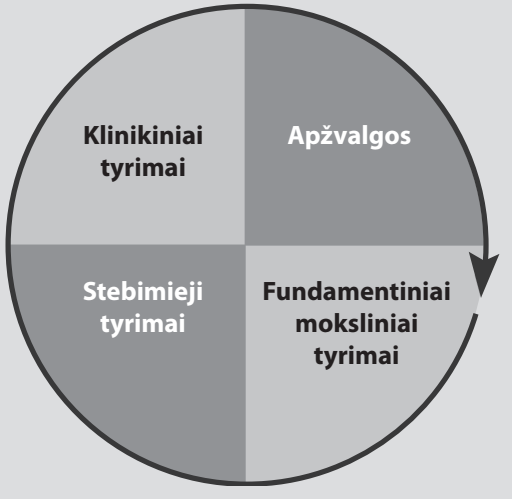
Tyrimo tikslas – apžvelgti įrodymus apie *Traumeel* vartojimą, remiantis pagrindinėmis registruotomis indikacijomis. Tyrimai, kurie apėmė neregistruotas indikacijas, netyrinėti.

METODAI

Rengiant šią apžvalgą, taikytas integruotas, „mišrių metodų“ požiūris, atsižvelgiant į turimus duomenis apie *Traumeel*. Toks metodas apėmė įrodymų lygmens klasifikavimą taikant vieną iš klasikinių hierarchinių įrodymų klasifikavimo sistemų, papildant ją nehierarchiniu turimų duomenų įvertinimu.

Siekiant įvertinti kiekvieno iš susijusių tyrimų įrodymų lygmenį, naudota OCEBM 2011 įrodymų lygio klasifikavimo sistema [1] gydymui įvertinti.

Nehierarchinei įrodymų klasifikacijai taikytos įrodymų mozaikos kategorijos, kaip parodyta 1 paveiksle. Įrodymų mozaiką [2] sudaro skirtingi tyrimo metodai, turintys savo pranašumų ir trūkumų.



***1 pav.* Įrodymų mozaika**

REZULTATAI

Buvo atrinkti dvidešimt du tyrimai. Tarp jų trys – Schneider [3], Müller-Löbnitz [4] ir Speed [5] – apžvalginiai straipsniai; šeši – Zell [6,7], Thiel [8,9], Böhmer [10], Arora [11], González de Vega [12] ir Lozada [13,14] – klinikiniai; septyni – Zenner [15,16], Weiser [17,18], Ludwig [19], Birnesser [20] ir Schneider [21,22] – perspektyvieji analitiniai stebėjimo; septyni – Conforti [23,24], Enbergs [25], Lussignoli [26], Heine [27], Porozov [28], Seilheimer [29] ir St. Laurent [30] – fundamentiniai moksliniai tyrimai.
Keturi susiję tyrimai neįtraukti dėl originalių tyrimo duomenų trūkumo. [31–34]

Pagrindinės įtrauktų *Traumeel* tyrimų charakteristikos, taip pat ir įrodymų lygmens klasifikavimas, remiantis OCEBM įrodymų lygmens klasifikavimo sistema, pateikiamas lentelėje.

Lentelė

Summary of the Main Characteristics of the Included Traumeel Studies and Evidence Grading[a]

Study design	First author (year)	Objective	Indication	Treatment investigated	N included/ analyzed patients[b]	Outcome assessment	Results	Main conclusion(s) authors	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	Variety of degenerative, traumatic and inflammatory conditions	Traumeel S injections in varying dosages	3241	5-point outcome scale ranging from "very good" to "worse" Any adverse effects	Osteoarthritis, sprains, and soft-tissue rheumatism were the most commonly treated conditions Therapy result assessed as "very good" or "good" in 79% of cases 19 reports of adverse effects, most commonly redness/irritation at injection site, no serious adverse events	Traumeel S in injectable form is a low-risk therapeutic option for the treatment of the consequences of traumata as well as inflammatory and degenerative processes affecting the musculoskeletal system	3
Prospective cohort study	Zenner (1994)[15]	To assess the effectiveness and safety of Traumeel S ointment as used in daily practice	Sprains, soft-tissue rheumatism, osteoarthritis	Traumeel S ointment in varying dosages	3422	5-point outcome scale ranging from "very good" to "worse" Any adverse effects	Sprains was the most common indication, followed by osteoarthritis, hematoma and various soft-tissue rheumatic conditions Therapy result assessed as "very good" or "good" in 87% of cases 13 reports of adverse effects, most commonly local skin reactions; 3 cases with more severe allergic reaction prompting termination of treatment	Traumeel S ointment is a low-risk therapeutic option for the treatment of the consequences of traumata as well as inflammatory and degenerative processes affecting the musculoskeletal system	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	Contusions, distortions, hemorrhages, osteoarthritis and soft-tissue rheumatism	Traumeel S drops and tablets in varying dosages	1359	5-point outcome scale ranging from "very good" to "worse" Any adverse effects	Sprains, bruises and post-traumatic hematoma were the most common acute indications. Osteoarthritis and various soft-tissue rheumatic conditions were the most common inflammatory/degenerative conditions Therapy result assessed as "very good" or "good" in around 80% of cases No adverse effects were observed Approximately two thirds of patients received adjuvant pharmacological or non-pharmacological treatment	Traumeel S in tablet or liquid oral form is a very well tolerated option for the treatment of the consequences of traumata as well as inflammatory and degenerative processes affecting the musculoskeletal system. Whilst it can be applied as a monotherapy, it has excellent applicability in combination with other pharmacological treatments due to the absence of interactions	3
Prospective cohort study	Ludwig (2001)[19]	To assess the effectiveness and safety of Traumeel S ointment as used in children in daily practice	Contusions, sprains, hematomas, and dislocations	Traumeel S ointment in varying dosages	157	5-point outcome scale ranging from "very good" to "worse" Any adverse effects	Contusions, sprains, hematomas, and dislocations were the most common indications. Therapy result assessed as "very good" or "good" in around 97% of cases No adverse effects were observed	Traumeel is effective in the treatment of both blunt trauma and muscle, joint, and soft-tissue disorders of varying etiology	3
Prospective comparative cohort study	Birnesser (2004)[20]	To compare the effectiveness of Traumeel S injections with standard NSAID therapy in patients with epicondylitis	Patients with diagnosed epicondylitis	Traumeel S injections in varying dosages NSAID injections in varying dosages up to 2 weeks	184	Local pressure pain, pain on movement, pain at rest on 5-point scale (no pain to severe) after 1 and 2 weeks Extensional and torsional joint mobility on 4-point scale (normal to heavily impaired) Test for non-inferiority (left border 97.5% Confidence Interval between group difference does not cross -0.4 for the pain scores and -0.3 for the mobility scores) after 2 weeks Tolerability	Traumeel was equivalent (non-inferior) to NSAIDs on all evaluated variables and statistically significantly superior to NSAIDs on pain at rest, torsional, and extensional joint mobility No adverse effects of Traumeel were reported (compared to 3 in NSAID group)	Traumeel S is a well-tolerated alternative to NSAIDS for the symptomatic treatment of epicondylitis	3

Study design	First author (year)	Objective	Indication	Treatment investigated	N included/ analyzed patients[b]	Outcome assessment	Results	Main conclusion(s) authors	OCEBM evidence level treatment benefits
Prospective comparative cohort study	Schneider (2005)[22]	To compare the effectiveness of Traumeel ointment with diclofenac gel in patients with tendinopathies	Patients with tendinopathies of varying etiology	Traumeel S ointment in varying dosages up to 28 days	357	Local pressure pain, pain at rest and on movement on a 4-point scale (no pain to severe pain) Mobility (pronation/supination, flexion/extension, abduction/adduction) on a 4-point scale (no pain to severe pain) Time to first symptomatic improvement Test for non-inferiority (left border one-sided 95% Confidence Interval between group difference does not cross -0.5)	Traumeel was non-inferior to diclofenac on all assessed variables Statistical adjustment for measured covariates took place No adverse effects of Traumeel were reported (compared to 1 in diclofenac group)	Traumeel was as effective and well tolerated compared to a commonly used NSAID gel	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	Sprains, strains, contusions of the ankles, knees, and hands	Traumeel S in varying dosages and galenic forms	133	Primary: Rate of resolution of principal and second symptoms at end of the (maximally 3 months) observation period. Time until symptomatic improvement Treatment outcome as assessed by physician	Rate of symptom resolution and time until symptom resolution were comparable between treatment groups No adverse events in Traumeel group (compared to 6 mild-to-moderate adverse events in the control group)	This study contributes to the case for a broad clinical effectiveness of Traumeel in the treatment of acute injuries and trauma	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	Acute ankle sprains	Traumeel S ointment, 10-12g under a compression bandage on days 1,3,5,8,10,12,14	73	Primary: Total flexion-extension angle of the affected ankle compared with the non-affected angle Treatment success defined as: Between-ankle flexion-extension angle difference after 10 days less than 10 degrees Secondary: Inversion (supination) angle of ankle; pain at movement	Treatment success after 10 days significantly higher in Traumeel group (52%) compared to placebo group (25%) No more pain at motion after 10 days significantly higher in Traumeel group (85%) compared to placebo group (36%) Between-ankle supination angle difference after 10 days < 7 degrees significantly higher in Traumeel group (75%) compared to placebo group (56%)	The improvement on the 10th day was significantly better in the Traumeel group compared to the placebo group	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	Post-traumatic bloody effusion of the knee joint	Traumeel N intra-articular injection, 2 ml at day 1, 4, and 8	80	Total flexion-extension angle difference between affected and non-affected knee (treatment success: ≤ 10 degrees) Knee circumference difference between affected and non-affected knee (treatment success: ≤ 0.5 cm) Pain at rest, motion, and pressure (3-point scale) Amount and character of synovial fluid at punction of the knee	Treatment success range of motion and knee circumference at day 8 significantly higher in Traumeel group (65%) compared to placebo group Pain sum scores at day 8 significantly lower in Traumeel group compared to placebo group Quicker cessation of bloody effusion in Traumeel group compared to placebo group	The efficacy of Traumeel injections is superior to saline injections	2
Randomized, placebo-controlled clinical trial	Böhmer (1992)[10]	Investigating the efficacy of Traumeel ointment in the treatment of various acute sport injuries	Contusions, sprains	Traumeel S ointment 6-10g twice daily for 15 days Traumeel minus (6 ingredient) version ointment	102	Primary: reduction of swelling and skin temperature Increase of maximum muscle force Reduction in pain intensity Time until resumption of training Overall effectiveness (patient and physician)	Results reported here concern 34 patients on Traumeel S in comparison with 34 on placebo Traumeel S was non-statistically significantly superior to placebo in reducing swelling after 15 days Reduction in skin temperature was similar between treatment groups Maximum muscle force at 15 days superior in Traumeel group compared to placebo Pain reduction superior in Traumeel group compared to placebo both at day 5 and 15 Resumption of training sooner in Traumeel group compared to placebo Assessment effectiveness by doctor and patients in Traumeel group superior to the placebo group Tolerability similar (good) in both treatment groups	Findings are positive and highly congruous compared to other studies	2

Study design	First author (year)	Objective	Indication	Treatment investigated	N included/ analyzed patients[b]	Outcome assessment	Results	Main conclusion(s) authors	OCEBM evidence level treatment benefits
Phase-1 type clinical trial	Arora (2000)[11]	Investigating the safety of orally applied Traumeel in healthy volunteers	n/a	Traumeel tablets 3 times daily for 28 days	20	Any clinical symptoms Complete blood cell count, liver profile, serum chemistry, bleeding time, coagulation time, GI bleeding (via testing for occult blood in stool) at follow-up compared to baseline	All adverse events were mild to moderate and resolved without intervention despite continued use of Traumeel No changes in any of the laboratory parameters	Traumeel is well tolerated and safe in healthy subjects No significant GI symptoms or toxicity Traumeel is a possible treatment alternative for patients at high risk of bleeding associated with NSAID use	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	Acute unilateral ankle sprain of the lateral ligaments	Traumeel ointment or gel, diclofenac gel (1%), 2g three times daily for up to 14 days	449	Primary: change from baseline to day 7 of maximum ankle pain (on VAS), and change from baseline to day 7 on the Foot and Ankle Ability Measure (FAAM). Non-inferiority analysis based on lower bound of 97.5% Confidence Interval (CI) above pre-defined inferiority margin of 0.4 Secondary: VAS and FAAM at different time points, FAAM sports subscale, swelling, global assessment of treatment efficacy	At all visits in the main treatment period, the 97.5% CI were above the predefined lower equivalence margin of 0.4 Possibly treatment-related adverse events reported in 3% (Traumeel ointment), 2% (Traumeel gel), and 2% (diclofenac gel) groups. The majority were mild or moderate in severity. No serious adverse event occurred	This study confirmed that Traumeel ointment and gel are non-inferior to diclofenac gel in the reduction of pain and restoration of function in individuals with mild-to-moderate acute ankle sprain Traumeel is a viable treatment option and alternative to topical diclofenac in the management of acute ankle sprain	2
Randomized, double blind, placebo-controlled clinical trial	Lozada (2014, 2015)[14,13] (abstracts)	Investigating the efficacy of intra-articular Traumeel and Zeel in patients with osteoarthritis of the knee	Moderate-to-severe chronic osteoarthritis of the knee	Traumeel S and Zeel T intra-articular injections every three weeks during a 17-week follow-up period	232	Primary: WOMAC Osteoarthritis Pain Subscale Secondary: Total WOMAC score, subscores for stiffness and physical function, change in pain following a 50ft walk, patient and physician global assessments	Traumeel and Zeel (TrZe) injections were significantly superior to saline from day 15 until day 99 with the exception of day 29 (borderline significant) on the WOMAC pain subscore. 50ft walk test superior in the TrZe group compared to the saline group. TOTAL WOMAC and stiffness and physical function subscores directionally similar to the WOMAC pain subscore. Adverse events were generally mild and unrelated to treatment. There were no therapy-related severe adverse events	TrZe injections provided statistically significant and clinically relevant pain relief on days 15 to 99 in comparison with placebo. TrZe injections are a safe and effective treatment for pain in moderate-to-severe knee osteoarthritis	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	Acute musculoskeletal injuries such as sprains, strains, tendinopathies, and stress fractures	Traumeel S in varying dosages and galenic forms	9017[b] (Traumeel treated patients across all studies)	Literature review on mechanisms of anti-inflammatory actions of Traumeel ingredients Narrative review of evidence of effects from clinical trials and observational studies	The basic literature on Traumeel and its ingredients is discussed in relation to the (patho) physiology of inflammation Identified randomized clinical trials (3) and non-randomized observational studies (6) are reviewed and discussed Safety data of all the identified studies are assessed and discussed	There is a growing evidence base supporting the effectiveness of Traumeel, either as a monotherapy or in combination with other medicinal or non-medicinal therapies. More randomized controlled studies are needed Traumeel is well tolerated There is a growing insight into the possible mechanism of action, particularly on immune cell function Traumeel may provide an alternative to NSAIDs as an alternative anti-inflammatory and analgesic agent	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	Registered indications: acute sports injuries, epicondylitis, tendinosis, rheumatoid arthritis	Traumeel S in varying dosages and galenic forms	9186[b]	Systematic literature search of the studies available on Traumeel Quality of randomized controlled trials assessed with the Jadad score Narrative review of the identified studies Narrative review of identified clinical studies of Traumeel constituents in phytotherapy and in micro- and ultra-low dilutions	The available evidence of the clinical efficacy and safety of Traumeel and its constituents is presented The suggested bioregulatory, immunomodulatory and anti-inflammatory mode of action of Traumeel and its constituents is detailed	Traumeel's efficacy and excellent safety profile warrant its consideration as a first-line treatment of physical trauma and sport injuries	n/a

Study design	First author (year)	Objective	Indication	Treatment investigated	N included/ analyzed patients[b]	Outcome assessment	Results	Main conclusion(s) authors	OCEBM evidence level treatment benefits
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	Acute and chronic/recurring soft-tissue disorders	Traumeel S in varying dosages and galenic forms	495[b] (Traumeel treated patients across all trials)	Literature review on pathophysiology and management of soft-tissue injuries including possibilities and limitations of NSAIDs Narrative review of evidence of effects from clinical trials	Risk-benefits of NSAIDs in pain management are reviewed Risks of pain masking for long-term recovery are discussed Arguments for multi-targeted approach to inflammation as part of pain management are given Narrative review of 5 RCTs of Traumeel S	Treatment algorithm developed by a group of international experts for the appropriate use of Traumeel in clinical practice is proposed Traumeel provides a different approach to the management of inflammation and consecutive pain	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	In vivo: rats with adjuvant arthritis or carrageenan-induced edema In vitro: neutrophils	In vivo: Traumeel injection intramuscular In vitro: Traumeel solution	n/a	In vivo: Swelling associated with acute and chronic inflammation In vitro: Neutrophil adhesion and superoxide anion production; platelet adhesion	None of the cellular functions in vitro showed a significant inhibition Traumeel reduced carrageenan-induced edema only when administered locally Traumeel did not significantly inhibit the adjuvant arthritis	Traumeel reduces the development of local edema Traumeel does not act like a conventional anti-inflammatory drug Traumeel appears to inhibit the acute inflammatory process locally	5
Basic research, in vitro	Enbergs (1998)[25]	Testing the effects of Traumeel on phagocyte and lymphocyte activity	n/a	n/a	n/a	Measuring phagocyte activity in whole (human) blood via chemiluminescence Activity and proliferation of lymphocytes via MTT test	Traumeel consistently induced noteworthy and highly significant stimulation reactions in the phagocytosis test Traumeel's effect on lymphocytes in MTT test was predominantly stimulating, but not very strong nor dose related	Consistent effects on phagocytosis suggest that Traumeel acts as an immunostimulant The effects on lymphocytes were less clear and consistent	5
Basic research, in vivo	Lussignoli (1999)	Testing the effects of Traumeel on traumatic blood extravasation	Blood-induced edema hind paw Sprague-Dawley rats	Traumeel S, plus its individual constituents: 1 h before or 30 min after edema induction	n/a	Edema volume Serum IL-6	Decrease of paw edema more rapid in Traumeel compared to saline This occurred in both treatment conditions (1h before and 30m after edema induction) Traumeel significantly reduced IL-6 production compared to saline	Traumeel appears to act via an acceleration of the healing process rather than via blocking of edema generation A not yet fully understood synergistic action between Traumeel components appears to occur	5
Basic research, in vitro ex vivo	Heine (2002)[27]	Investigating the anti-inflammatory action of Traumeel	n/a	Traumeel S, 15 drops 3 times daily for 14 days in rheumatoid arthritis patients	n/a	Assessing TGF-β production via the measurement in the blood of changes in (TGF-β producing) Th3 lymphocytes of 10 patients with early-stage rheumatoid arthritis after treatment with Traumeel	7 out of 10 patients displayed an increase, or a large increase in the number of Th3 after treatment	The authors propose a possible working mechanism (referred to as the immunological bystander reaction) in which antihomotoxic medicines serve as a trigger for re-establishing normal immune tolerance via the generation of Th3 cells	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	n/a	Traumeel S	n/a	T-cell and monocyte proliferation Effects on pro-inflammatory mediators, IL-1β (from gut epithelial cells), TNF-α (from T-cells), and IL-8 (from monocytes) over a period of 24-72h	Traumeel inhibited the secretion of all three pro-inflammatory mediators, both in resting and activated state Effects appeared to be inversely dose-related (lower dilutions exhibiting higher inhibition) Traumeel exerted no effect on T-cell and monocyte proliferation	Traumeel does not inhibit immune cell functions via a direct (toxic) effect The inversely dose-dependent effects suggest an immuno-modulatory effect of Traumeel	5
Basic research, in vitro	Seilheimer (2009)[29]	Investigating the effects of Traumeel S on chondrocytes and human matrix metalloproteinases	n/a	Traumeel S	n/a	Chondrocyte proliferation and viability (MTT assay and 3H-Thymidine incorporation) Chondrocyte functional activity (sGAG via dimethylene blue assay) Human matrix metalloproteinase (MMP) activity (chromogenic assay)	Traumeel enhanced induced chondrocyte proliferation, but not basal proliferation Traumeel enhanced viability of chondrocytes (in differentiated state) and stimulated sGAG biosynthesis Traumeel selectively inhibited some MMPs (i.e., MMP-13) but not others (MMP 2,3, and 9)	Traumeel supported the differentiation of chondrocytes Traumeel inhibited MMP-13, which is associated with pathological joint destruction, and may therefore indirectly slow down the progression of cartilage degeneration	5

Study design	First author (year)	Objective	Indication	Treatment investigated	N included/ analyzed patients[b]	Outcome assessment	Results	Main conclusion(s) authors	OCEBM evidence level treatment benefits
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	n/a	Traumeel S in a high and low dose	n/a	Transcriptome analysis at 12 to 192 hours post wound-induction, using high throughput Helicos RNA deep sequencing Various analyses, including a suite of Systems Biology analyses	Traumeel induced gene-expression changes in the TGF-β pathway and associated extracellular matrix genes Traumeel affected the gene-expression of growth factor and tissue generation pathways	Traumeel induced a broad range of transcriptome changes during the wound healing time course The findings suggest that Traumeel is a natural multitarget therapy in inflammatory conditions	5

[a] Evidence grading in accordance with the OCEBM Levels of Evidence Schedule1

[b] Number of subjects in review papers may also be included in other mentioned studies in the Table.

Lentelė rodo, kad *Traumeel* naudą patvirtina tokie lygmens įrodymai: šeši klinikiniai tyrimai priskiriami 2 įrodymų lygmeniui; septyni stebimieji tyrimai priskiriami 3 įrodymų lygmeniui, o septyni fundamentiniai moksliniai tyrimai – 5 įrodymų lygmeniui. Trys apžvalginiai straipsniai, pateikti 1 lentelėje, nepriskirti 1 įrodymų lygmeniui, nes nė viena iš apžvalgų nebuvo sisteminė ir todėl neatitiko 1 įrodymų lygmens kriterijų.

Lentelė demonstruoja, jog galimi tyrimai su vietiškai vartojamomis, peroralinėmis ir injekuojamomis vaisto formomis. Vartojimo indikacijos apima ūmius patempimus, pertempimus bei sumušimus, reumatologinio pobūdžio nusiskundimus, susijusius su minkštųjų audinių pažaida, pavyzdžiui, esant epikondilitui, tendinitui, bursitui ir kt., taip pat lėtines degeneracines ligas – osteoartritą bei reumatoidinį artritą. Tad gali būti išskiriami trys indikacijų tipai: ūmūs pažeidimai, reumatologiniai nusiskundimai, susiję su minkštųjų audinių pažaida, bei lėtinės degeneracinės reumatologinės ligos.

Iš šešių tyrimų, priskiriamų 2 įrodymų lygmeniui, keturi apima ūmius skeleto ir raumenų sistemos pažeidimus (trys ūmius patempimus / sumušimus, vienas – potrauminį kraujo išsiliejimą į kelio sąnarį), vienas – kelio sąnario osteoartritą. Dar viename pateikiami duomenys iš 1 fazės klinikinio tyrimo, kuriame tiriamas peroralinių *Traumeel* formų saugumas.

Į Zell [6,7] ir González de Vega [12] atliktus tyrimus įtraukti pacientai (besiskundę ūmiais čiurnos patempimais), kurie tyrimo metu lyginti su kontrolinių grupių ligoniais, gavusiais placebą (Zell), ir aktyvaus gydymo kitų preparatų (González de Vega). Böhmeret et al [10] placebu kontroliuojamame tyrime dalyvavo pacientai, turintys daugybinių sporto traumų, todėl tiriamąją imtį sudarė ne tik išskirtiniai pacientai, kuriems nustatyti čiurnos patempimai. Thiel et al [8,9] tyrimas apėmė potrauminio kraujo išsiliejimo į kelio sąnarį gydymą. Tyrimas atliktas griežtai laikantis aklumo principo. Jis parodė objektyvius gydymo *Traumeel* skirtumus pastarojo preparato naudai, palyginti su placebu.

Lozada et al [13,14] tyrimas nustatė *Traumeel* kombinacijos su *Zeel* naudą, palyginus su placebu, pacientų akimis nesiskiriančiu nuo vaistinio preparato, gydant kelio sąnario osteoartritą, o gydymo efektyvumui vertinti taikant patvirtintą baigčių skalę. Arora [11] 1 fazės tyrimas patvirtino peroralinės *Traumeel* formos vartojimo saugumą sveikiems pacientams.

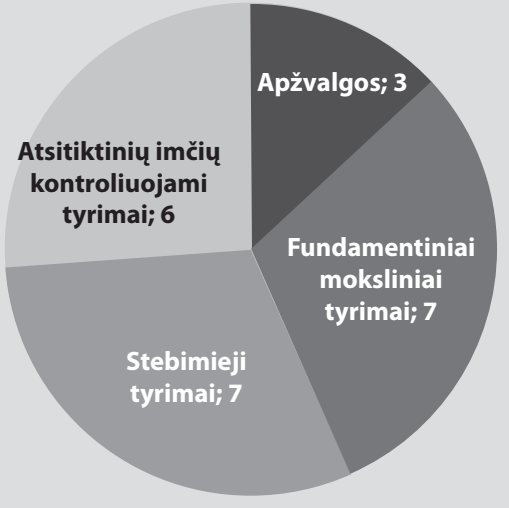
Septyni analitiniai stebėjimo tyrimai priskirti 3 įrodymų lygmeniui. Trys iš šių tyrimų buvo didelės apimties perspektyvieji analitiniai stebėjimo tyrimai, kurie apėmė visus tris minėtus indikacijų tipus. Į du tokius tyrimus įtraukti pacientai, besiskundžiantys ūmiais čiurnos patempimais ir sumušimais, o dar du tyrimai apėmė reumatologines minkštųjų audinių patologijas (epikondilitą ir tendinitą). Visi šie tyrimai parodė, kad skirtingų *Traumeel* vaistinių formų vartojimas kasdienėje praktikoje buvo efektyvus ir saugus.

Septyni ikiklinikiniai (4 *in vitro*, 3 *in vivo*) tyrimai priskirti 5 įrodymų lygmeniui. Dauguma šių tyrimų parodė, jog *Traumeel* gali veikti kaip daugiakomponentis, daugelį taikinių moduliuojantis vaistas. Įvairūs *in vitro* ir *in vivo* tyrimai patvirtino, kad *Traumeel* pasižymi antiuždegiminiu ar labiau „uždegimą reguliuojančiu“ poveikiu bei neturi įtakos prostaglandinų sintezės keliui. Tai rodo (ir patvirtina klinikinius duomenis), jog *Traumeel* gali būti saugi alternatyva NVNU. Seilheimer et al [29] chondrocitų tyrimas *in vitro* leidžia daryti išvadą, kad *Traumeel* slopina metaloproteazes, kurios susijusios su patologine sąnario destrukcija. Heine et al [27] *in vitro ex-vivo* tyrimas rodo, jog *Traumeel* gali turėti įtakos atkuriant normalią imuninę toleranciją pacientams, sergantiems reumatoidiniu artritu. Inovatyvus St. Laurent et al [30] tyrimas, kurio metu taikyta didelio našumo transkriptomo analizė, patvirtino, kad *Traumeel* veikia uždegimo kaskados augimo faktorių genų ekspersiją ir kitų procesų audiniuose kelius, kuriuos galima stebėti žaizdos gijimo modelyje.

Taigi, yra nemažai 2 lygmens įrodymų, jog *Traumeel* efektyvus gydant ūmius patempimus. Be to, pateikiama keletas 2 lygmens įrodymų, kad *Traumeel* galėtų būti naudingas gydant ūmias kelio sąnario traumas, taip pat ir kelio sąnario osteoartritą. *Traumeel* efektyvumą ūmių patempimų atvejais papildomai patvirtina penki analitiniai stebėjimo tyrimai, priskiriami 3 įrodymų lygmeniui pagal tas pačias indikacijas.

Traumeel efektyvumo gydant reumatologines minkštųjų audinių patologijas įrodymai yra silpni ir daugiausia patvirtinami dviem palyginamaisiais analitiniais stebėjimo tyrimais, kurie priskiriami 3 lygmens įrodymams. Taip pat yra nemažai 5 lygmens įrodymų, kurie demonstruoja, jog *Traumeel* veikia kaip uždegimą reguliuojantis vaistas per įvairius, įskaitant ir audinių regeneracijos, kelius.

Traumeel įrodymų mozaikos kategorijos pateikiamos 2 paveiksle.



***2 pav. Traumeel* įrodymų mozaikos diagrama**

2 paveikslas demonstruoja, jog įrodymus apie *Traumeel* veiksmingumą remia daugelis įvairių tyrimų. Papildomą reikšmę suteikia duomenų sutapimas tarp įvairių šaltinių. Pavyzdžiui, klinikinių tyrimų duomenys apie *Traumeel* efektyvumą ūmių čiurnos patempimų atvejais yra papildomi ne vienu stebimuoju tyrimu, patvirtinančiu šio vaistinio preparato efektyvumą bei saugumą.

Trys apžvalginiai straipsniai, paminėti lentelėje, įtraukti į įrodymų mozaiką. Nors šie tyrimai neatitiko 1 OCEBM įrodymų lygmens kriterijų, jie naudingi ir papildo įrodymų mozaiką. Pavyzdžiui, Müller-Löbnitz [4] apžvalginiame straipsnyje vertinami ir turimi duomenys apie *Traumeel*, ir atskiros *Traumeel* sudedamosios dalys. Nors pastarasis straipsnis nesuteikia tiesioginių įrodymų apie *Traumeel*, tačiau patvirtina tam tikrus faktus, remiančius įrodymus. Panašiai ir Schneider et al [3] apžvalginiame straipsnyje nagrinėjama literatūra apie *Traumeel*, jo ingredientus, kartu aptariant jų poveikį uždegimo patofiziologijai, ryšį su ja. Speed et al [5] apžvalgoje daugiausia aptariamos minkštųjų audinių patologijos, taip pat jų patofiziologija, ir šių būklių valdymas taikant ir *Traumeel*. Todėl vertinant turimus ikiklinikinius ir klinikinius duomenis patofiziologiniame bei klinikiniame kontekste, šis straipsnis papildo *Traumeel* poveikio įrodymų mozaiką,

Esant skirtingoms traumoms poveikis, pastebėtas atliekant įvairius ikiklinikinius tyrimus, visiškai sutampa su besiplečiančiomis žiniomis apie daugybinius kelius, įtrauktus į uždegimo reguliaciją, bei kitus mechanizmus, susijusius su gijimo procesu. Kaip buvo pastebėta skirtingų klinikinių tyrimų metu, uždegimo įtraukimas į įvairius patologinius procesus, taip pat ir gijimas po įvairių ūmių traumų logiškai paaiškina platų *Traumeel* efektyvumą.

APTARIMAS

Yra patikimų įrodymų, kad *Traumeel* veiksmingas gydant ūmius patempimus. Be to, pateikiama palankių įrodymų gydant osteoartritą, reumatoidinį artritą bei kelio traumą, esant skysčio susikaupimui sąnario ertmėje, taip pat ir esant lėtinėms būklėms, pvz., epikondilitui ir tendinitui. Pasirodo, jog *Traumeel* kaip daugiakomponentis vaistas veikia įvairiais būdais. Todėl jo ir veikimo mechanizmas, ir saugumas biologiškai tikėtinesnis, nei iš vieno pagrindinio komponento sudaryti, vieną taikinį veikiantys vaistai (tokie kaip NVNU).

Nors per pastaruosius 30 metų apie *Traumeel* buvo surinkta daug mokslinių duomenų, reiktų paminėti tam tikras įrodymų silpnybes ir poreikį jas patobulinti. Įrodymai apie *Traumeel* veiksmingumą turėtų būti toliau stiprinami atliekant tyrimų duomenų sistemines analizes. Reikėtų apsvarstyti metaanalizės atlikimo galimybę, įtraukiant tris esamus tyrimus apie ūmius patempimus / sumušimus. Böhmer et al [10] tyrimas apėmė pacientus, patyrusius įvairias viršutinių ir apatinių galūnių sporto traumas (ir sumušimus, ir patempimus). Dėl šio heterogeniškumo *Traumeel* ir placebo grupės palygintos nevisiškai. Lozada et al [13,14] tyrimas apėmė gydymą *Traumeel* kartu su kitu homeopatiniu preparatu. Dėl to nustatytas poveikis negali būti priskirtas vien tik *Traumeel*, nors tai buvo aukštos kokybės tyrimas su nedidele paklaidos rizika. Heine et al [27] *in vitro* tyrimo trūkumas – maža imtis ir tinkamos kontrolės stoka. Todėl ir šio tyrimo rezultatus reiktų vertinti atsargiai.

Tad turimi duomenys leidžia daryti išvadą, jog įrodymų apie *Traumeel* bazė plečiasi ir įgauna įvairių aspektų. Mūsų nuomone, tokia integruota ir daugialypė turimų duomenų analizė yra puikus pacientų priežiūros informavimo šaltinis.

LITERATŪRA

1. Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence. CEBM Web site. http://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf. Accessed February 22, 2017.
2. van Haselen R. Medical study formats: an overview. *J Biomed Ther*. 2010;4(2):26-27.
3. Schneider C. Traumeel: an emerging option to nonsteroidal anti-inflammatory drugs in the management of acute musculoskeletal injuries. *Int J Gen Med*. 2011;4:225-234. doi:10.2147/ijgm.s16709.
4. Müller-Löbnitz C, Göthel D. Review of the clinical efficacy of the multicomponent combination medication Traumeel and its components. *Altern Ther Health Med*. 2011;17(suppl 2):S18-S31.
5. Speed C, Wolfarth B. Challenges of pain masking in the management of soft tissue disorders: optimizing patient outcomes with a multi-targeted approach. *Curr Med Res Opin*. 2014;30(5):953-959. doi:10.1185/03007995.2014.913412.
6. Zell J, Connert WD, Mau J, Feuerstake G. Treatment of acute sprains of the ankle: a controlled double-blind trial to test the effectiveness of a homeopathic ointment. *Biol Ther*. 1989;7(1):1-6.
7. Zell J, Connert WD, Mau J, Feuerstake G. Behandlung von Sprunggelenksdistorsionen: Doppelblindstudie zum Wirksamkeitsnachweis eines homöopathischen Salbenpräparats. *Fortschr Med*. 1988;106(5):96-100.
8. Thiel W, Borho B. The treatment of recent traumatic blood effusions of the knee joint. *Biol Ther*. 1994;12(4):242-248.
9. Thiel W, Borho B. Posttraumatische Kniegelenksergüsse und intraartikuläre Traumeel-N-Injektion. *Orthopädische Prax*. 1991;27(11):721-725.
10. Böhmer D, Ambrus P. Treatment of sports injuries with Traumeel ointment: a controlled double-blind study. *Biol Ther*. 1992;10(4):290-300.
11. Arora S, Harris T, Scherer C. Clinical safety of a homeopathic preparation. *Biomed Ther*. 2000;18(2):222-225.
12. González de Vega C, Speed C, Wolfarth B, González J. Traumeel vs. diclofenac for reducing pain and improving ankle mobility after acute ankle sprain: A multicentre, randomised, blinded, controlled and non-inferiority trial. *Int J Clin Pract*. 2013;67(10):979-989. doi:10.1111/ijcp.12219.
13. Lozada C, del Rio E, Reitberg DP, Smith R, Moskowitz RW. Risk-benefit of co-administered Traumeel® (Tr14) and Zeel® (Ze14) intra-articular (IA) injections in patients with moderate-to-severe pain associated with OA of the knee (OAK) (THU0441). *Ann Rheum Dis*. 2015;74(suppl 2):4268. doi: 10.1136/annrheumdis-2015-eular.426810.
14. Lozada C, del Rio E, Reitberg D, Smith R, Kahn C, Moskowitz RW. A multi-center double-blind, randomized, controlled trial (db-RCT) to evaluate the effectiveness and safety of co-administered Traumeel® (Tr14) and Zeel® (Ze14) intra-articular (IA) injections versus IA placebo in patients with moderate-to-severe pain associated with OA of the knee. *Arthritis Rheum*. 2014;66(suppl):S1266.
15. Zenner S, Metelmann H. Therapy experiences with a homeopathic ointment: Results of drug surveillance conducted on 3,422 patients. *Biol Ther*. 1994;12(3):204-211.
16. Zenner S, Metelmann H. Application possibilities of Traumeel S injection solution: Results of a multicentric drug monitoring trial conducted on 3,241 patients. *Biol Ther*. 1992;10(4):301-310.
17. Zenner S, Weiser M. Oral treatment of traumatic, inflammatory, and degenerative conditions with a homeopathic remedy. *Biomed Ther*. 1997;15(1):22-26.
18. Weiser M, Zenner S. Orale Therapie traumatischer, entzündlicher und degenerativer Affektionen mit einem Homöopathikum. *Biol Medizin*. 1996;25(5):211-216.
19. Ludwig J, Weiser M. Treating pediatric trauma with a homeopathic ointment. *J Biomed Ther*. 2001;(2):8-11.
20. Birnesser H, Oberbaum M, Klein P, Weiser M. The homeopathic preparation Traumeel S compared with NSAIDs for symptomatic treatment of epicondylitis. *J Musculoskelet Res*. 2004;8(2 & 3):119-128. doi:10.1142/S0218957704001284.
21. Schneider C, Schneider B, Hanisch J, van Haselen R. The role of a homoeopathic preparation compared with conventional therapy in the treatment of injuries: an observational cohort study. *Complement Ther Med*. 2008;16(1):22-27. doi:10.1016/j.ctim.2007.04.004.
22. Schneider C, Klein P, Stolt P, Oberbaum M. A homeopathic ointment preparation compared with 1% diclofenac gel for acute symptomatic treatment of tendinopathy. *Explore (NY)*. 2005;1(6):446-452. doi:10.1016/j.explore.2005.08.010.
23. Conforti A, Bertani S, Lussignoli S, Bellavite P. Wirkungen Antihomotoxischer Präparate auf akute und chronische Entzündungen. *Biol Medizin*. 1998;27(2):63-66.
24. Conforti A, Bertani S, Metelmann H, Chirumbolo S, Lussignoli S, Bellavite P. Experimental studies on the anti-inflammatory activity of a homeopathic preparation. *Biomed Ther*. 1997;15(1):28-31.
25. Enbergs H. The effect of selected potentiated suis organ preparations and Traumeel on phagocyte and lymphocyte activity. *Biomed Ther*. 1998;16(2):178-185.
26. Lussignoli S, Bertani S, Metelmann H, Bellavite P, Conforti A. Effect of Traumeel S, a homeopathic formulation, on blood-induced inflammation in rats. *Complement Ther Med*. 1999;7(4):225-230.
27. Heine H, Andrä F. On the anti-inflammatory mechanism of action of an antihomotoxic compound remedy [in German]. *Ärztezeitschrift für Naturheilverfahren*. 2002;43(2):96-104.
28. Porozov S, Cahalon L, Weiser M, Branski D, Lider O, Oberbaum M. Inhibition of IL-1β and TNF-α secretion from resting and activated human immunocytes by the homeopathic medication Traumeel® S. *Clin Dev Immunol*. 2004;11(2):143-149. doi:10.1080/10446670410001722203.
29. Seilheimer B, Wierzchacz C, Gebhardt R. Influence of Traumeel on cultured chondrocytes and recombinant human matrix metalloproteinases: implications for chronic joint diseases. *Eur J Integr Med*. 2009;1(4):252-253.
30. St. Laurent G, Tackett M, McCaffrey T, Kapranov P. Deep sequencing transcriptome analysis of Traumeel therapeutic action in wound healing (THU0016). *Ann Rheum Dis*. 2013;72(suppl 3). doi:10.1136/annrheumdis-2013-eular.544.
31. Wolfarth B, González de Vega C, Kapranov P, St Laurent G, Speed C. Inflammation in soft tissue disorders: the evidence and potential role for a natural multi-target medication. *Curr Med Res Opin*. 2013;29(suppl 2):1-2. doi:10.1185/03007995.2013.779874.
32. Speed C, González de Vega C. Treatment of musculo-skeletal inflammatory disorders using a clinically proven medication with a novel mechanism of action. *Ann Rheum Dis*. 2011;70(suppl 3):685.
33. Cesnulevicius K. The bioregulatory approach to work-related muskuloskeletal disorders: using the multicomponent ultra low-dose medication Traumeel to target the multiple pathophysiological processes of the disease. *Altern Ther Health Med*. 2011;17(suppl 2):S8-S17.
34. Orchard JW, Best TM, Mueller-Wohlfahrt HW, et al. The early management of muscle strains in the elite athlete: best practice in a world with a limited evidence basis. *Br J Sports Med*. 2008;42(3):158-159. doi:10.1136/bjsm. 2008.046722.
35. González de Vega C, Gonzáles J. A randomized, controlled, multicenter study on the effectiveness of Traumeel (ointment and gel) in terms of pain reduction and function improvement compared with diclofenac gel in acute ankle sprain. *Ann Rheum Dis*. 2012;71(suppl 3):SAT0423.