Review

Therapeutic Potential of Tranilast, an Anti-allergy Drug, in Proliferative Disorders

MOSHE ROGOSNITZKY[1], RACHEL DANKS[2] and ELENA KARDASH[2]

[1]*MedInsight Research Institute, Telz Stone, Israel;*
[2]*MedInsight Research Institute, Island West, Steep, U.K.*

Abstract. *Tranilast (N-[3,4-dimethoxycinnamoyl]-anthranilic acid; Rizaben®) is an anti-allergy drug approved for use in Japan and South Korea, also used against asthma, autoimmune diseases, and atopic and fibrotic pathologies. The antitumor potential of tranilast is attracting considerable interest. This review summarizes recent evidence concerning the effect of tranilast on different tumor types and discusses the drug's possible mode of action in this area. In vivo and in vitro studies are covered, as well as evidence from clinical trials, in which tranilast was evaluated in various models of proliferative disorders. The findings presented in this report, demonstrate the excellent potential of tranilast in the management of certain types of tumor, and provide a strong rationale for the initiation of controlled clinical trials in this area.*

Tranilast (N-[3,4-dimethoxycinnamoyl]-anthranilic acid; Rizaben®) has been approved in Japan and South Korea, since 1982, for the treatment of bronchial asthma, with indications for keloids and hypertrophic scar added in 1993. Tranilast is also used to treat asthma, autoimmune diseases, atopic and fibrotic pathologies, and can also inhibit angiogenesis (1, 2).

The antiproliferative properties of tranilast were discovered in the late 1980s, when it was found that tranilast elicited an inhibitory effect on fibroblast proliferation *in vitro* and also suppressed collagen production both *in vitro* and *in vivo* (3, 4). Follow-up studies revealed that tranilast also reduced the release of chemical mediators from mast cells and suppressed hypersensitivity reactions (5-7).

This article is freely accessible online.

Correspondence to: Moshe Rogosnitzky, MedInsight Research Institute, P.O. Box 386. Telz Stone, 90840, Israel. E-mail: moshe@medinsight.org

Key Words: Tranilast, proliferative disorders, keloid tumors, tumor microenvironment, mast cells, TGF-β signaling, cell cycle, apoptosis, review.

Subsequent studies have confirmed the ability of tranilast to inhibit cancer cell growth and proliferation in various tumor models, including breast, pancreatic and prostate cancer, as well as glioma and other tumors (8-10).

The discovery of the antiproliferative potential of tranilast prompted additional studies directed at understanding the mechanisms of tranilast action, revealing that its inhibitory effect on cell proliferation depends principally on the capacity of tranilast to interfere with transforming growth factor beta (TGF-β) signalling (11, 12). Another potential mechanism of tranilast-mediated inhibition of cell proliferation involves the down-regulation of chemokine production by mast cells and the inhibition of matrix metalloproteinase (MMP) secretion (11, 13).

Evidence supporting the antiproliferative potential of tranilast has accumulated over the past three decades from *in vitro* and *in vivo* studies combined with a small number of case reports and clinical investigations. However, although tranilast appears to have relatively low toxicity (5), little is known concerning its mode of action in the human body, or regarding the full scope of its effects when administered to patients suffering from proliferative disorders. One of the reasons for the scarcity of data is the lack of a systematic approach directed at investigating the effect of tranilast in the clinical setting.

In this review, we summarize the information available on the effect of tranilast in various *in vitro* and *in vivo* models for proliferative disorders. We also present data from clinical studies and case reports on tranilast in tumors and keloid scars, and discuss the possible mechanisms of action of tranilast.

In order to identify relevant studies for this review, a literature search of peer-reviewed papers published between 1976 and 2010, was conducted using the GoPubMed database and the Google Scholar search engine. Only articles published in English were considered for the review, with the exception of one case report on keloid tumors and hypertrophic scars by Nanba *et al*. (14), which was translated

from Japanese. The combinations of key-words used to perform the online searches are listed in Table I.

Instead of exhaustively and indiscriminately presenting the findings of every tranilast study published to date, we have identified representative highlights of all studies available, to provide a more focused discussion on the available evidence.

Table I. *Results of literature search for tranilast in proliferative disorders.*

Key words	Number of hits
Tranilast + cancer	34
Tranilast + apoptosis	22
Tranilast + TGF-β signaling	62
Tranilast + prostate	3
Tranilast + keloids	24
Tranilast + matrix metalloproteinases	12

Preclinical Findings

Following the initial discovery of the antiproliferative potential of tranilast in the late 1980s (4, 15), a number of follow-up studies addressing the effect of tranilast on uncontrolled cell proliferation in various *in vivo* and *in vitro* models were performed. Highlights of these studies are presented below, and are summarized in Table II.

In Vitro Findings

Prostate cancer. Osteoblastic bone metastasis, driven in part by osteoclast differentiation stimulated by TGF-β production from bone stromal cells, is a common complication of prostate cancer (16). Inhibition of TGF-β–mediated signaling is therefore a major therapeutic target (16).

Izumi *et al.* showed that tranilast applied to three prostate cancer cell lines led to a dose-dependent reduction in cell proliferation by inducing cell cycle arrest and by promoting apoptosis (12). Further experiments revealed that tranilast treatment suppressed TGF-β-induced differentiation of bone-derived stromal cells and also inhibited TGF-β release from different cell types, including the bone-related cells (12).
Sato *et al.* showed that tranilast (0.1 and 1 mM) significantly reduced cell proliferation in all prostate cancer cell lines examined, and increased the rate of apoptosis in the LNCaP and PLS-10 cell lines (17).

Glioma. Platten *et al.* employed an *in vitro* model to demonstrate that tranilast treatment suppresses migration and invasiveness of the human malignant glioma cell lines LN-18 and T98G (11). This study showed that the growth-inhibitory effect of tranilast is concentration-dependent, and that the tranilast treatment caused inhibition of DNA synthesis and induced p21 accumulation without causing cytotoxicity. Furthermore, the study provided evidence for tranilast-dependent reduction in TGF-β release by glioma cells. Finally, the work demonstrated that tranilast treatment inhibited cell migration, chemotactic responses and invasiveness of glioma cells *in vitro* (11).

Breast cancer. Several studies have addressed the effect of tranilast on uncontrolled cell proliferation in both *in vitro* and *in vivo* breast cancer models. Two studies (18, 19) provide clear evidence for an antitumor effect of tranilast *in vitro* through the inhibition of both cell proliferation and cell cycle progression in several mammary carcinoma cell lines, including the human lines MDA-MB-231, MCF-7, and BT-474 (18, 19). These studies showed that tranilast inhibits cell proliferation, by blocking cell cycle progression and also down-regulates TGF-β signaling. Furthermore, Chakrabarti *et al.* demonstrated that tranilast inhibits the mitogen-activated protein kinase (MAPK) signaling pathway, which is known to be implicated during the epithelial to mesenchymal transition (EMT), accompanying tumor cell invasion (18).

A later study by Subramaniam *et al.* found that tranilast inhibited the migration of BT-474 and MDA-MBA-231 cells by reducing their motility, as demonstrated in a wound-healing assay (20).

Importantly, tranilast was also shown to be effective against chemotherapy-resistant cancer stem cells (CSCs). In a study performed by Prud'homme *et al.*, tranilast inhibited the formation of mammospheres in CSCs, generated by the incubation of the MDA-MB-231 human breast cancer line in the presence of mitoxantrone (21). Tranilast also lowered the expression of stem cell markers in these CSCs.

Neurofibroma. In a study conducted by Yamamoto *et al.*, tranilast (10 to 100 μM) was added to fibroblasts and Schwann NF1 cells, co-cultured with mast cells, to closely reproduce the physiological environment of neurofibroma and was found to significantly reduce the proliferation of NF1 cells (22). In addition, TGF-β production and release of stem cell factor and of tryptase from the mast cells was reduced.

Gastric carcinoma. Yashiro *et al.* addressed the effect of tranilast on the invasiveness of the gastric carcinoma cell line OCUM-2D, in the presence of the gastric fibroblast cell line NF-10. Tranilast treatment at concentrations higher than 0.01 mM significantly reduced the invasive potential of OCUM-2D in the presence of NF-10 fibroblasts (23).

Uterine leiomyoma. Shime *et al.* investigated the role of tranilast in inhibiting the proliferation of uterine leiomyoma cells *in vitro* (10). This study revealed that tranilast (10-300 μM) suppressed the proliferation of cultured human leiomyoma cells in a dose-

dependent manner. The antiproliferative activity of tranilast was associated with the inhibition of cell cycle regulators such as cyclin-dependent kinase 2 (CDK2). Importantly, no cytotoxic effect was observed upon treatment with tranilast.

Pancreatic cancer. Hiroi *et al*. demonstrated that tranilast (>25 μg/ml) significantly inhibited cell proliferation in the hamster pancreatic cancer cell line PGHAM-1 (9). The application of tranilast (50 μg/ml) also inhibited DNA synthesis, and induced an accumulation of cells in the G_0 phase.

In a study by Mitsuno *et al*., the effect of tranilast on the sensitivity of human pancreatic cancer cell lines to various anticancer agents was investigated and tranilast was found to enhance the sensitivity of KP4 cell line to gemcitabine (24). The increased sensitivity was associated with the reduced expression of ribonucleotide reductase M1 (RRM1), suggesting that the mechanism of action of tranilast includes RRM1 down-regulation (24).

In Vivo Findings

Prostate cancer. Sato *et al*. studied the effect of tranilast treatment on prostate cancer cell growth and osteoclast differentiation using a rat *in vivo* model. Tranilast (200 mg/kg/day or 400 mg/kg/day) was administered following transplantation of rat prostate carcinomas onto cranial bones of 6-week-old male F344 rats. High-dose tranilast resulted in a significant reduction in tumor volume, due to induction of apoptosis and necrosis in tumor tissues, rather than inhibition of proliferation. Moreover, tranilast inhibited osteoclast differentiation of rat bone marrow cells (17).

Izumi *et al*. applied tranilast (100 or 200 mg/kg/day) to severe combined immunodeficiency (SCID) mice implanted with LANCaP-SF prostate cancer cells and found that tranilast reduced the tumor volume in a dose-dependent manner (12). Furthermore, tranilast applied at 300 mg/kg/day significantly inhibited osteoclastic changes in three out of nine treated mice.

Breast cancer. Chakrabarti *et al*. administered tranilast (300 mg/kg/day) to the mammary fat pads of 6-week-old BALB/c mice implanted with highly metastatic murine 4T1 cells and showed reduction in primary tumor growth of up to 50% (18). Moreover, metastasis of the transplanted cells to the lung was reduced by more than 90%, following tranilast exposure.

In a follow-up study by Prud'homme *et al*., the inhibitory effect of tranilast on uncontrolled proliferation of human chemotherapy-resistant CSCs, implanted into mouse mammary fat pads was demonstrated and tranilast (300 mg/kg/day for 3 weeks) was shown to inhibit lung metastasis of MDA-MB-231 cells injected intravenously into NOD-SCID gamma mice (21).

Pancreatic carcinoma. Hiroi *et al*. showed that tranilast (25 μg/ml) inhibited tumor angiogenesis in response to vascular endothelial growth factor, significantly reducing the microvessel density at the metastatic site, in a hamster dorsal air sac model (9).

Oral squamous cell carcinoma (OSCC). In a study by Noguchi *et al*., tranilast (4 mg/animal) was administered daily by intraperitoneal injection into a mouse model of OSCC, prepared by implanting OSC-19 cells into BALB/c nude mice. Three weeks of tranilast treatment significantly reduced the tumor growth and inhibited the incidence of cervical lymph node metastasis (25).

Clinical Findings

A limited number of clinical investigations is available regarding the effect of tranilast on tumors. Individual case studies of successful treatment of tumors and keloid scars with tranilast have also been reported. All these clinical investigations involve patients from Japan or South Korea, where tranilast is approved for medical use for other conditions. Details are summarized in Table III.

Clinical Studies

Prostate cancer. Two clinical studies by Izumi *et al*. indicated a potential for tranilast to alleviate complications associated with prostate cancer. In the initial study, four out of 16 patients with advanced hormone-refractory prostate cancer (HRPC), treated with oral tranilast (300 mg/day) showed a reduction in prostate-specific antigen (PSA) levels, suggesting that tranilast could be used to improve prognosis in patients with advanced HRPC (12). In the 2010 follow-up pilot study, 21 Japanese patients with advanced castration-resistant prostate cancer (CRPC) were treated with oral tranilast (300 mg/day) for a median period of five months (26). Continuous PSA inhibition was observed in three patients, lasting 4-13 months. In another two patients, PSA elevation was inhibited for one month following initiation of tranilast therapy. Overall survival rates at 12 and 24 months were 74.5% and 61.5%, respectively.

Keloid scars. A dose-ranging study by Nanba *et al*. conducted over 12 weeks in 263 Japanese patients established the optimal dose of 5 mg/kg/day, for the treatment of keloid and hypertrophic scarring. Patients treated at this dose were observed to have an improvement rate of 64.7%, with a low rate of adverse events (14).

Case Reports

Vulval syringoma. The first successful treatment of the rare disorder, vulval syringoma, was reported in a case study by Iwao

Table II. *Laboratory investigations (in vitro and in vivo models).*

Tumor type	Model system	Effect	Pathway	Reference
Mouse mammary carcinoma	4T1 cell line	Inhibition of EMT transition; induction of apoptosis	TGF-β signalling down-regulation; p53 up-regulation	18
Rat mammary carcinoma	LA7 cell line	Inhibition of cell proliferation		
Human breast carcinoma	MDA-MB-231 and MCF-7 cell lines	G_1/S cell cycle arrest		
Human breast carcinoma	*In vitro*			
	MDA-MB-231 and BT-474 cell lines and CSCs	Inhibition of colony and mammosphere formation by tranilast treatment (200 μM)	Suppression of RB phosphorylation and reduction in expression levels of CSC markers: CD133 and OCT-4	21
	In vivo			
	Chemotherapy-resistant MDA-MB-231 cells injected into mouse pad or intravenously to induce lung metastasis	Suppression of primary tumor growth; prevention of lung metastasis		
Human breast carcinoma	MDA-MB-231 BT-474	Apoptosis induction	PARP cleavage	20
Prostate cancer	*In vitro*			
	Human cell lines: LNCaP LNCaP-SF PC-3	Tranilast application at 0-300 μmol/l inhibited cell proliferation in a dose-dependent manner; apoptosis induction; cell cycle arrest	Inhibition of TGF-β-stimulated differentiation of bone-derived stromal cells; Inhibition of TGF-β secretion by bone-derived stromal cells	12
	In vivo			
	SCID mice	Inhibition of tumor growth as measured by reduction in tumor volume, inhibition of osteoblastic changes in 3 out of 9 mice		
Prostate cancer	*In vitro*			
	Human cell lines: LNCaP PC-3 DU145 Rat cell line: PLS-10	Reduction in cell proliferation	Up-regulation of phospho-GSK3b and down-regulation of phospho-AKT	17
	In vivo			
	Rat prostate cancer tissue transplanted into cranial bones of F344 rats. Tranilast treatment: 200-400 mg/kg per day	Reduction in tumor volume, induction of apoptosis and tumor necrosis		
Glioma	*In vitro*			
	LN-18 and T98G human malignant glioma cells	Inhibition of proliferation, migration, chemotactic responses and invasiveness	Inhibition of DNA synthesis Accumulation of p21	
	In vivo			
	9L rat glioma		Reduction of TGF-β release by glioma cells	11
Human gastric carcinoma cell line	OCUM-2D	Tranilast treatment (>0.01mM) reduced cell growth	Inhibition of TGF-β production, invasiveness of OCUM-2D cells and MMP2 secretion	23
Gastric fibroblast cell line	NF-10			
Uterine leiomyoma	Human primary culture cell line	Inhibition of cell proliferation	G_1 cell cycle arrest associated with induction of $p21^{waf1}$ and p53	10
Keloid scars	*In vivo*, hairless rat	Transdermal delivery effective in relieving pain and itching	Not applicable	29
Neurofibromas	*In vitro*, cell culture treated with 10-100 μM of tranilast	Reduction in tumor proliferation	TGF-β signalling down-regulation	22

Table II. *Continued*

Table II. *Continued*

Tumor type	Model system	Effect	Pathway	Reference
Pancreatic cancer	*In vitro* Human pancreatic cell lines: KP4, PK-8, PK9, PK-59	Induced sensitivity to gemcitabine	Decrease in the expression of RRM1	27
Pancreatic cancer	*In vitro* Hamster pancreatic cell line PGHAM-1 *In vivo* Five-week old Syrian golden hamsters	Inhibition of proliferation and colony formation in a dose-dependent manner Reduction in tumor angiogenesis	Inhibition of DNA synthesis, cell cycle arrest	9
Oral squamous cell carcinoma	*In vitro* OSC-19 cell line *In vivo* OSC-19 cells implanted into a tongue of BALB/c nude mice	No effect on cell proliferation Reduction in tumor growth and metastasis	Not reported	25

CSCs: cancer stem cells; DNA: deoxyribonucleic acid; EMT: epithelial to mesenchymal transition; MMP: matrix metalloproteinase; PARP: poly(ADP-ribose)polymerase; RB: retinoblastoma; RRM1: ribonucleotide reductase M1; SCID: severe combined immunodeficiency; TGF-β: transforming growth factor beta.

Table III. *Clinical studies (reported case studies).*

Tumor type	Patients	Treatment and observed effect	Reference
CRPC	21 Japanese patients with advanced HRPC	Oral tranilast (300 mg/day) for 5 months resulted in reduction in PSA levels.	26
Vulval syringoma	26-year-old Japanese woman	Tranilast treatment (300 mg/day) for 6 months successfully reduced tumor, leading to its eventual disappearance.	27
Hypertrophic scars	Four patients with hypertrophic scars	Tranilast was administered transdermally using ionophoretic method (12 mg dissolved in 1.5 ml of ethanol/water mixture), reduction in skin reddening and itching was observed	29
Keloid scars	Double-blind clinical study consisting of 263 Japanese patients	An optimal dose of tranilast for treatment of keloid and hypertrophic scars was determined as 5 mg/kg/day.	14
Desmoid tumor of the chest	48-year-old Japanese man	Tranilast administered orally at a dose of 300 mg per day resulted in clearance of the tumor.	28
Solitary mastocytomas	Case 1: 10-month-old Japanese boy with 3 months' history of plaque on his right shoulder.	Tranilast was administered orally at 5 mg/kg/day for 2.5 years in combination with a steroid (diflorasone diacetate, 0.05%, topical application, for 8 weeks) for duration of 4 months; reduction in wheal appearance within the first two weeks of treatment, the plaque disappeared after 8 weeks of treatment; no recurrence was observed after treatment termination during the two-year follow-up period	
	Case 2: 4-month-old Japanese girl with one month history of plaque on her left chest	Tranilast was applied at 5 mg/kg/day in combination with a steroid for duration of 4 months; reduction in wheal and bulla formation after two weeks of treatment, the plaque faded after two months of treatment leaving faint pigmentation; no recurrence was observed after treatment termination during the one-year follow-up period.	30

CRPC: Castration-resistant prostate cancer; HRPC: hormone-resistant prostate cancer; PSA: prostate-specific antigen.

Table IV. *Adverse reactions reported in 21,772 test administrations of tranilast (36).*

System	Event	n (%)
Gastrointestinal	Nausea	53 (0.24)
	Stomach ache	45 (0.21)
	Reduced appetite	28 (0.13)
Liver and bile duct	Elevated ALP	25 (0.11)
	Abnormal liver function	92 (0.42)
	Elevated GOT	31 (0.14)
	Elevated GPT	33 (0.15)
Anaphylaxis	Rash	33 (0.15)
Urinary	Frequent urination	12 (0.06)
	Blood in urine	8 (0.04)

ALP: Alkaline phosphatase; GOT: glutamate-oxaloacetate transaminase; GPT: glutamic pyruvic transaminase.

et al. reporting on a 26-year-old Japanese woman treated with tranilast (300 mg/day) for six months. A significant reduction in papule size was observed after three weeks. After six months, the tumor had disappeared and no recurrence was observed (27).

Desmoid tumor of the chest. Goto *et al*. reported a case study in which a 48-year-old Japanese male patient presenting with a desmoid tumor in his chest was treated with oral tranilast (3×100 mg/day) (28). The tumors' size began to decrease after six months of treatment, after 2.2 years the tumor was impalpable, and there was no recurrence at two years after treatment discontinuation.

Keloid scars. Shigeki *et al*. reported several case studies involving tranilast treatment in patients suffering from hypertrophic scars (29). Tranilast was administered transdermally into the affected areas of four different patients (12 mg in 1.5 ml ethanol/water). In every patient, tranilast treatment eased both the itching and the pain associated with hypertrophic scars; however, in some cases, these symptoms returned after an unspecified period.

Mastocytoma in infants. Katoh *et al*. reported the successful treatment of mastocytoma in a Japanese infant boy, aged 10 months and a girl aged four months, treated with oral tranilast (5 mg/kg/day in three divided doses) (30). In both cases, the plaque resulting from uncontrolled proliferation disappeared, or was significantly reduced eight weeks after the initiation of tranilast treatment.

Molecular Mechanisms of Tranilast Action

Several important pathways, including those regulating cellular proliferation, growth, cell cycle, and cell migration, have been identified as potential targets of tranilast.

A known mechanism underlying the antitumor activity of tranilast involves the blocking of the release of chemical mediators from mast cells, thereby suppressing hypersensitivity reactions (1, 5-7). This has been confirmed by a recent study by Yamamoto *et al*., in which tranilast suppressed the proliferation of tumor cells by inhibiting cell-growth promoting pathways and also by blocking the production of chemical mediators released by mast cells (22). A study by Suzawa *et al*. showed that tranilast also inhibited the release of interleukin-1 beta (IL-1β) from monocytes/macrophages, thus slowing down the rate of fibroblast proliferation and, as a result, tranilast down-regulated the formation of keloids and hypertrophic scars (15).

TGF-β signaling. An important signaling pathway targeted by tranilast treatment is the TGF-β-regulated signaling cascade. Numerous *in vitro* and *in vivo* studies have indicated the inhibitory effect of tranilast on TGF-β-mediated signaling and also on TGF-β secretion (11, 12, 18, 23). One of the results of tranilast interference with TGF-β signaling is manifested in the reduction of collagen synthesis by keloid fibroblasts (3).

Anti-metastatic potential of tranilast treatment. Subramaniam *et al*. showed that cell lysates obtained from tranilast-treated cells contained reduced levels of the metastatic marker endoglin and MMP9 (19). It has also been shown that such reduction is associated with an inhibition of TGF-β signaling (19).

DNA synthesis, cell proliferation, and apoptosis. Tranilast treatment has been demonstrated in various cancer cell lines *in vitro,* to lead to a reduction in cell proliferation, including breast, prostate, pancreatic carcinoma, and other tumor cell lines (12, 18, 19). The inhibitory effect of tranilast on cell proliferation has been repeatedly linked to its ability to interfere with cell cycle progression, arresting cells in the G_0/G_1 transition (2, 9, 10, 19).

Induction of apoptosis and cell cycle arrest upon tranilast treatment has been reported for several breast and prostate cancer cell lines (12, 19). Two studies by Subramaniam *et al*. explored the molecular pathways involved in the apoptosis induction, resulting from tranilast treatment. One of the studies showed that tranilast applied to murine mammary carcinoma cells leads to p53 up-regulation, enhanced phosphorylation of the serine-threonine protein kinase (AKT1), and reduced phosphorylation of extracellular regulated kinase 2 (ERK2) (19). In another work from the same group, an increased level of a poly(ADP-ribose) polymerase (PARP)-cleavage product, was detected in human cancer cell lines exposed to tranilast (20).

Another mechanism through which tranilast induces cell cycle arrest is likely to employ inhibition of calcium influx, a process which is normally required for G_1/S progression. It

has been demonstrated in MCF-7 cells, that calcium entry initiated by insulin-like growth factor 1 (IGF-1) was blocked by tranilast treatment in a dose-dependent manner (31).

Another molecular target of tranilast has been identified to be the aryl hydrocarbon receptor (ARH) (32). ARH's function has previously been implicated in anticancer effects (33, 34), and an ARH presence in the cell was necessary for tranilast-mediated cell cycle arrest. Tranilast acts as an ARH agonist and leads to ARH translocation to the nucleus. A possible mechanism described by Prud'homme *et al*. involves weaker binding of ARH to CDK4, resulting in a reduced level of phosphorylation and cell cycle arrest in retinoblastoma (21).

EMT and cell migration. Cancer cells rely on EMT in order to form metastases. Two independent studies using different model systems have demonstrated that tranilast treatment down-regulates EMT-associated cellular behavior (18, 35). Tranilast treatment inhibited the migration of cancer cells in wound-healing assays, with the reduced motility of cells correlating with the levels of expression of a global cytoskeleton regulator myocardin-related transcription factor A (MRTF-A) (19, 20).

Safety and Pharmacokinetics

Tranilast exhibits relatively low toxicity in patients (2, 5, 14, 26), making this drug a very attractive candidate for future clinical investigations. Out of 21,772 test administrations, 679 adverse reactions in 513 cases were reported (2.36%) (36). These events are summarized in Table IV.

Discussion

The preclinical and clinical data of tranilast suggest this agent is a promising candidate with the capacity for treating proliferative disorders. Its low toxicity and apparent effectiveness in suppressing cell proliferation, migration, and invasiveness, as demonstrated in a number of *in vitro* and *in vivo* models of proliferative disorders, emphasize the therapeutic potential of tranilast.

Major signaling pathways, such as TGF-β signaling, apoptotic pathways, and pathways controlling cell cycle progression, have been identified as main targets of tranilast. The emerging role of tranilast in inhibiting the secretion of certain MMPs makes it an attractive candidate that could act as an inhibitor of cell invasion during metastasis. A capacity to inhibit cytokine secretion from mast cells (11, 12, 18, 23), indicates yet another pathway implicated in the ability of tranilast to inhibit cell proliferation.

Despite promising *in vitro* and *in vivo* research data, supporting the potential of tranilast as an antiproliferative agent, considerable research on its action in the human body is still required to confirm this potential.

To further validate the available data and to fully establish the mechanism of action of tranilast, additional *in vivo* studies, combined with systematic clinical investigations are essential. It is of particular importance to verify clinical observations and case studies in a broader selection of patients.

Conclusion

Based on the clinical and preclinical studies reviewed here, tranilast appears as a promising, safe and effective agent in treating certain antiproliferative disorders. However, comprehensive clinical studies are necessary to further explore its potential and its mechanisms of action in various clinical conditions.

Acknowledgments

The Authors thank Ms. Rieko Konitzer for translating the original manuscripts from Japanese.

References

1 Azuma H, Banno K and Yoshimura T: Pharmacological properties of N-(3',4'-dimethoxycinnamoyl) anthranilic acid (N-5'), a new anti-atopic agent. Br J Pharmacol *58*: 483-488, 1976.

2 Isaji M, Miyata H and Ajisawa Y: Tranilast A New Application in the Cardiovascular Field as An Antiproliferative Drug. Cardiovascular Drug Reviews *16*: 288-299, 1998.

3 Yamada H, Tajima S, Nishikawa T, Murad S and Pinnell S R: Tranilast, a selective inhibitor of collagen synthesis in human skin fibroblasts. J Biochem *116*: 892-897, 1994.

4 Isaji M, Nakajoh M and Naito J: Selective inhibition of collagen accumulation by N-(3,4-dimethoxycinnamoyl)anthranilic acid (N-5') in granulation tissue. Biochem Pharmacol *36*: 469-474, 1987.

5 Koda A, Nagai H, Watanabe S, Yanagihara Y and Sakamoto K: Inhibition of hypersensitivity reactions by a new drug, *N*(3',4'-dimethoxycinnamoyl) anthranilic acid (N-5'). J Allergy Clin Immunol 57: 396-407, 1976.

6 Koda A, Kurashina Y and Nakazawa M: The inhibition mechanism of histamine release by N-(3,4-dimethoxycinnamoyl) anthranilic acid. Int Arch Allergy Appl Immunol *77*: 244-245, 1985.

7 Komatsu H, Komatsu H, Kojima M, Tsutsumi N, Hamano S, Kusama H, Ujiie A, Ikeda S, and Nakazawa M: Study of the mechanism of inhibitory action of tranilast on chemical mediator release. Jpn J Pharmacol *46*: 43-51, 1988.

8 Yashiro M, Chung, Y S and Sowa M: Tranilast (N-(3,4-dimethoxycinnamoyl) anthranilic acid) down-regulates the growth of scirrhous gastric cancer. Anticancer Res *17*: 895-900, 1997.

9 Hiroi M, Onda M, Uchida E and Aimoto T: Antitumor effect of N-[3,4-dimethoxycinnamoyl]-anthranilic acid (tranilast) on experimental pancreatic cancer. J Nippon Med Sch *69*: 224-234, 2002.

10 Shime H, Kariya M, Orii A, Momma C, Kanamori T, Fukuhara K, Kusakari T, Tsuruta Y, Takakura K, Nikaido T, and Fujii S: Tranilast inhibits the proliferation of uterine leiomyoma cells *in vitro* through G 1 arrest associated with the induction of p21(waf1) and p53. J Clin Endocrinol Metab *87*: 5610-5617, 2002.

11 Platten M. Wild-Bode C, Wick W, Leitlein J, Dichgans J, and Weller M: *N*-[3,4-Dimethoxycinnamoyl]-anthranilic acid (tranilast) inhibits transforming growth factor-beta relesase and reduces migration and invasiveness of human malignant glioma cells. Int J Cancer *93*: 53-61, 2001.
12 Izumi K. Mizokami A, Li YQ, Narimoto K, Sugimoto K, Kadono Y, Kitagawa Y, Konaka H, Koh E, Keller ET, and Namiki M. Tranilast inhibits hormone-refractory prostate cancer cell proliferation and suppresses transforming growth factor beta1-associated osteoblastic changes. Prostate *69*: 1222-1234, 2009.
13 Shimizu T, Kanai K, Asano K, Hisamitsu T and Suzaki H: Suppression of matrix metalloproteinase production in nasal fibroblasts by tranilast, an antiallergic agent, *in vitro*. Mediators Inflamm *3*: 150-159, 2005.
14 Nanba K, Oura T, Soeda S, Sioya N, Tsukada S, and Hanaoka K. Clinical evaluation of tranilast for keloid and hypertrophic scarring. Optimal dose finding study in a double blind study. Nessho 18: 30-45, 1992.
15 Suzawa H, Kikuchi S, Ichikawa K and Koda A: Inhibitory action of tranilast, an anti-allergic drug, on the release of cytokines and PGE-2 from human monocytes-macrophages. Jpn J Pharmacol *60*: 85-90, 1992.
16 Padua D and Massagué J: Roles of TGFbeta in metastasis. Cell Res 19: 89-102, 2009.
17 Sato S, Takahashi S, Asamoto M, Naiki T, Naiki-Ito A, Asai K, Shirai T: Tranilast suppresses prostate cancer growth and osteoclast differentiation *in vivo* and *in vitro*. Prostate *70*: 229-238, 2010.
18 Chakrabarti R, Subramaniam V, Abdalla S, Jothy S and Prud'homme GJ: Tranilast inhibits the growth and metastasis of mammary carcinoma. Anticancer Drugs *20*: 334-345, 2009.
19 Subramaniam V, Chakrabarti R, Prud'homme GJ and Jothy S: Tranilast inhibits cell proliferation and migration and promotes apoptosis in murine breast cancer. Anticancer Drugs *21*: 351-361, 2010.
20 Subramaniam V, Ace O, Prud'homme GJ and Jothy S: Tranilast treatment decreases cell growth, migration and inhibits colony formation of human breast cancer cells. Exp Mol Pathol *90*: 116-122, 2011.
21 Prud'homme GJ, Glinka Y, Toulina A, Ace O, Subramaniam V, and Jothy S: Breast cancer stem-like cells are inhibited by a non-toxic aryl hydrocarbon receptor agonist. PLoS One *5*: e13831, 2010.
22 Yamamoto M, Yamauchi T, Okano K, Takahashi M, Watabe S, and Yamamoto Y: Tranilast, an anti-allergic drug, down-regulates the growth of cultured neurofibroma cells derived from neurofibromatosis type 1. Tohoku J Exp Med *217*: 193-201, 2009.
23 Yashiro M, Murahashi K, Matsuoka T, Nakazawa K, Tanaka H, Osaka H, Koyama T, Ohira M, and Chung KH: Tranilast (*N*-3,4-dimethoxycinamoyl anthranilic acid): a novel inhibitor of invasion-stimulating interaction between gastric cancer cells and orthotopic fibroblasts. Anticancer Res *23*: 3899-3904, 2003.
24 Mitsuno M Kitajima Y, Ohtaka K, Kai K, Hashiguchi K, Nakamura J, Hiraki M, Noshiro H, and Miyazaki K: Tranilast strongly sensitizes pancreatic cancer cells to gemcitabine via decreasing protein expression of ribonucleotide reductase 1. Int J Oncol *36*: 341-349, 2010.
25 Noguchi N, Kawashiri S, Tanaka A, Kato K and Nakaya H: Effects of fibroblast growth inhibitor on proliferation and metastasis of oral squamous cell carcinoma. Oral Oncol *39*: 240-247, 2003.
26 Izumi K, Mizokami A, Shima T, Narimoto K, Sugimoto K, Kobori Y, Maeda Y, Konaka H, Koh E and Namiki M: Preliminary results of tranilast treatment for patients with advanced castration-resistant prostate cancer. Anticancer Res *30*: 3077-3081, 2010.
27 Iwao F, Onozuka T and Kawashima T: Vulval syringoma successfully treated with tranilast. Br J Dermatol *153*: 1228-1230, 2005.
28 Goto T, Nemoto T, Ogura K, Hozumi, T and Funata N: Successful treatment of desmoid tumor of the chest wall with tranilast: a case report. J Med Case Rep *4*: 384, 2010.
29 Shigeki S, Murakami T, Yata N and Ikuta Y: Treatment of keloid and hypertrophic scars by iontophoretic transdermal delivery of tranilast. Scand J Plast Reconstr Surg Hand Surg *31*: 151-158, 1997.
30 Katoh N, Hirano S and Yasuno H: Solitary mastocytoma treated with tranilast. J Dermatol *23*: 335-339, 1996.
31 Nie L, Oishi Y, Doi I, Shibata H and Kojima I: Inhibition of proliferation of MCF-7 breast cancer cells by a blocker of Ca(2+)-permeable channel. Cell Calcium *22*: 75-82, 1997.
32 Kerkvliet NI: AHR-mediated immunomodulation: the role of altered gene transcription. Biochem Pharmacol *77*: 746-760, 2009.
33 Zhang S Lei P, Liu X, Li X, Walker K, Kotha L, Rowlands C, and Safe S: The aryl hydrocarbon receptor as a target for estrogen receptor-negative breast cancer chemotherapy. Endocr Relat Cancer *16*: 835-844, 2009.
34 Hall J. M Barhoover MA, Kazmin D, McDonnell DP, Greenlee WF, and Thomas RS: Activation of the aryl-hydrocarbon receptor inhibits invasive and metastatic features of human breast cancer cells and promotes breast cancer cell differentiation. Mol Endocrinol *24*: 359-369, 2010.
35 Kaneyama T, Kobayashi S, Aoyagi D and Ehara T: Tranilast modulates fibrosis, epithelial-mesenchymal transition and peritubular capillary injury in unilateral ureteral obstruction rats. Pathology *42*: 564-573, 2010.
36 RIZABEN data sheet (translated from Japanese). Available from http://www.gent.gifu.med.or.jp/gent/AntiAllergyDrugs/Rizaben.htm (Accessed 18 July 2011).

Received February 23, 2012
Revised April 6, 2012
Accepted April 9, 2012