Acta Derm Venereol 2015; 95: 778–782

SPECIAL REPORT

Intralesional 5-Fluorouracil in Keloid Treatment: A Systematic Review

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In the 1990s, 5-flourouracil (5-FU) was introduced as a treatment for keloids; however, there is still no consensus on its use. In order to guide clinical practice, a systematic review of the clinical evidence on the effectiveness of 5-FU in keloid treatment was carried out. Eight databases were searched on 10 September 2014 using the terms "keloid" and "5-FU", together with all synonyms of these terms. Two reviewers selected original research reports using 5-FU alone or combined with a maximum of 2 other therapies. Eighteen papers were found that reported either on intralesional 5-FU alone, or on 5-FU combined with triamcinolone acetonide (TAC:5-FU) or excision, including 482 patients. 5-FU treatment was effective in 45–96% of patients, but only TAC:5-FU may perform better than TAC alone. Due to a poor level of evidence, further research should establish the superiority of repeated intralesional TAC:5-FU injections over TAC alone with several doses and injection schedules. ***Key words: keloid; pathologic scar; 5-fluorouracil; treatment; corticosteroid.***

Accepted Mar 19, 2015; Epub ahead of print mar 25, 2015

Acta Derm Venereol 2015; 95: 778–782.

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Excessive scarring is a burden for both patients and specialists. Keloids are painful and itchy and, together with their aesthetic burden, have a major impact on patients' quality of life. Although they are benign lesions, they grow into healthy surrounding skin and resemble malignant growth patterns. There are wide differences in phenotype due to differences in the location, amount and size of the raised, pigmented, pruritic and painful lesions (1, 2). There are many treatments currently in use for keloids; silicone dressings are least invasive, but strong and reliable evidence for its efficacy is lacking. Corticosteroid injections have been the mainstay of treatment, but are not effective in all cases. More invasive therapy, such as cryosurgery or conventional surgery with additional corticosteroids or radiotherapy, unfortunately has a high risk of side-effects, recurrence and deterioration (1–4). High levels of therapy resistance, risk of recurrence, and the wide variety of treatment options all mean that treatment of keloids is challenging.

The resemblance of keloids to malignant growth patterns was used in searching for other minimally invasive, low-risk treatments; this led us to the chemotherapeutic drug 5-fluorouracil (5-FU). 5-FU blocks synthesis of the pyrimidine thymidine, which is a nucleoside necessary for DNA replication. Scarcity of thymidine monophosphatase results in thymidineless death in rapidly dividing cells (5). 5-FU has already proved effective and safe in the treatment of glaucoma, another benign condition (6). Even though there is no consensus on its value, 5-FU is used internationally to treat keloids. We therefore performed a systematic literature review on the effectiveness of treatment of keloids with 5-FU.

METHODS

In order to collect all available evidence EMBASE, MEDLINE, Web of Science, Scopus, CINAHL, the Cochrane Library, Google Scholar and PubMed Publisher were searched on 10 September 2014, using the terms "keloid" and "5-fluorouracil" together with all synonyms of these terms (i.e. search term EMBASE #1 Keloid: 'keloid'/exp OR keloid*:ti,ab OR cheloid*:ti,ab; #2 5-fluorouracil: 'Fluorouracil'/exp OR 'fluorouracil':ti,ab OR '5 fluorouracil':ti,ab OR '5fluorouracil':ti,ab OR '5 FU':ti,ab OR '5FU':ti,ab OR Adrucil:ti,ab OR Carac:ti,ab OR Efudex:ti,ab OR Fluoroplex:ti,ab; #3: #1AND#2).

Original research reports of randomized controlled trials (RCTs), prospective clinical trials and case series involving keloid treatment using intralesional 5-FU alone or combined with a maximum of 2 other therapies were included. We put no limitations on the date of publication, the age, gender, ethnicity of study participants, or the duration of disease. Exclusion criteria were: case reports ($n \leq 2$), animal studies, studies combining more than 3 different treatments, and language other than English.

First, 2 reviewers (SS, EB) independently assessed the titles and abstracts of potentially eligible studies. In cases of no agreement, a third reviewer (FBN) decided whether the article should be selected. Two reviewers independently extracted data from full-text copies of all selected studies. To identify other relevant studies, the reference lists of all included studies were examined (Fig. S1[1]).

We extracted patient characteristics, treatment protocol, and outcomes that were reported as recurrence rates, the percentage of observer-rated reduction or improvement, the percentage of

[1]https://doi.org/10.2340/00015555-2106

Table I. *Overview of studies using intralesional 5-fluorouracil injections or intralesional 5-fluorouracil/triamcinolone acetonide combined injections in keloid treatment*

Reference (year)	Treatment used	Patients/ keloids, *n*	Evidence level[a]	Definition keloid	Measurement method	Conc. (mg/ml)	Max dose/ injection (mg)	Injections, *n*	Injection interval, weeks	Follow-up[b], weeks	Outcome	Recurrence, %
Intralesional 5-fluorouracil injections												
Gupta & Kalra (2002) (21)	5-FU	24 P, 39 K	4–	NR	NR	50	150	16	1	>38	16.6% poor, 25% fair, 25% good, 33.3% excellent flattening[c]	0
Manuskiatti & Fitzpatrick (2002) (14)	5-FU	10 P	2b–	NR	R	50	NR	10	2	32	On average good flattening[c] Patient self-assessment: 70% fair, 30% good improvement	0
	RCT control TAC:5-FU	10 P				1:45	NR	10	2	32	On average good flattening[c] Patient self-assessment: 10% poor, 40% fair, 50% good improvement	0
	RCT control TAC	10 P				20	NR	6	4	32	On average excellent flattening[c] Patient self-assessment: 30% fair, 40% good, 30% excellent improvement	0
Nanda & Reddy (2004) (23)	5-FU	28 P	2b	R	NR	50	100	12	1	24	7.1% poor, 14.3% fair, 71.4% good 7.1% excellent improvement[d]	0
Kontochristopoulos, et al. (2005) (22)	5-FU	20 P	4–	NR	NR	50	100	±7	1	52	5% no, 10% poor, 40% fair, 40% good, 5% excellent improvement[d]	47
Mutalik & Patwardhan (2008) (25)	5-FU	24 P	4–	R	NR	50[e]	75	4	4	52	33% no/poor, 67% excellent flattening[c]	25
Sadeghinia & Sadeghinia (2012) (10)	5-FU	20 P	1b–	NR	R	50 T	NR	3	4	44	On average good flattening[c] Patient self-assessment: 15% fair, 35% good, 50% excellent improvement[d]	NR
	RCT control TAC	20 P				40	NR	3	4	44	On average good flattening[c] Patient self-assessment: 15% poor, 45% fair, 35% good, 5% excellent improvement[d]	NR
Sharma et al. (2012) (13)	5-FU	25 K	1b	R	R	50	NR	±10	1/2/4[f]	52	12% poor, 16% fair, 40% good, 32% excellent flattening[c]	0
	RCT control TAC:5-FU	25 K				4:45	NR	±10	1/2/4[f]	52	0% poor, 4 % fair, 44% good, 52% excellent flattening[c]	0
Saha & Mukhopadhyay (2012) (12)	5-FU	20 P	1b	NR	R	50	100	±5	1	56	0% no, 15% poor, 20% fair, 55% good, 10% excellent flattening[c]	35
	RCT control TAC	24 P				40	80	± 4	1	56	0% no, 8% poor, 25% fair, 54% good, 13% excellent flattening[c]	36
Prabu (2012) (11)	5-FU	14 P	1b	NR	R	50	100	4	1	29	0% no–poor, 36% fair, 50% good, 14% excellent flattening[c]	NR
	RCT control TAC	15 P				40	80	4	1	29	0% no–poor, 13% fair, 40% good, 47% excellent flattening[c]	NR
Intralesional 5-fluorouracil/triamcinolone acetonide combined injections												
Manuskiatti & Fitzpatrick (2002) (14)	TAC:5-FU	10 P	2b–	NR	R	1:45	NR	10	2	32	On average good flattening[c] Patient self-assessment: 40% fair improvement and 50% good improvement	0
	RCT control 5-FU	10 P				50	NR	10	2	32	On average good flattening[c] Patient self-assessment: 70% fair, 30% good improvement.	0
	RCT control TAC	10P				20	NR	6	4	32	On average excellent flattening[c] Patient self-assessment: 30% fair, 40% good, 30% excellent improvement[d]	0
Darougheh et al. (2007) (8)	TAC:5-FU	20 P	2b–	NR	R	4:45	8:90	8	1	12	On average good flattening[c] Patient self-assessment: 45% fair, 55% good improvement[c]	NR
	RCT control TAC	20P				10	20	8	1	12	On average good flattening (70%)[c] Patient self-assessment: 20% poor, 60% fair, 20% good improvement[d]	NR
Davison et al. (2009) (18)	TAC:5-FU	52 K	4	NR	R	10:37.5	NR	3	4	2–313	On average excellent flattening (81%)[c]	NR
Sharma et al. (2012) (13)	TAC:5-FU	25 K	1b	R	R	4:45	NR	±10	1/2/4[f]	52	0% poor, 4% fair, 44% good, 52% excellent flattening[c]	0
	RCT control 5-FU	25 K				50	NR	±10	1/2/4[f]	52	12% poor, 16% fair, 40% good, 32% excellent flattening[c]	0
Khan et al. (2014) (15)	TAC:5-FU	25 P	2b	NR	R	4:45	8:90	8	1	26	32% no–poor, 68% good–excellent improvement[d]	0
	RCT control TAC	33 P				10	20	8	1	26	39% no–poor, 61% good–excellent improvement[d]	0

[a]Level of evidence rated by Centre for Evidence-Based Medicine criteria, March 2009 (www.cebm.net). [b]From 1st injection. [c]No 0%, poor 1–25%, fair 26–50%, good 51–75%, excellent 76–100% keloid flattening. [d]No 0%, poor 1–25%, fair 26–50%, good 51–75%, excellent 76–100% keloid improvement. [e]In cases of inflamed or hard keloids TAC (40 mg/ml) was added to injection ratio 1:1, and silicone dressings were used for 3 months. [f]Injections were weekly for 4 weeks, then bimonthly for 2 months, then monthly. K: keloids; NR: not reported; P: patients; R: reported; T: tattooed; 5-FU: 5-fluorouracil; TAC: triamcinolone acetonide; RCT: randomized controlled trial.

patient-rated improvement, and the presence of side-effects. The outcomes were converted into 5 levels: no response; 1–25% as poor; 26–50% as fair; 51–75% as good; and 76–100% as excellent improvement or flattening of keloids. The quality of included studies was assessed on the basis of reproducibility and study design.

RESULTS

The literature search identified 286 references to keloid and 5-FU. After the selection process, 18 articles were included for critical appraisal. Two papers reported on the same cohort of patients; 1 of them was excluded (7, 8). The other reasons for exclusion are given in Fig. S1[1]. Among the references of the included articles no new original research papers were found.

In 1999, Fitzpatrick was the first to report on his wide experience with 5-FU in keloids, although not in a scientific setting (9). His publication prompted others to start collecting evidence. A total of 482 patients participated in 17 studies dating from 2001 to 2014. These studies examined several different methods of treatment with 5-FU. To evaluate the efficacy of 5-FU, we used the outcomes of 3 types of treatment: intralesional 5-FU alone, 5-FU combined with triamcinolone acetonide (TAC), and excision with 5-FU with or without TAC (Tables I and II).

5-FU efficacy in keloid treatment

The use of intralesional 5-FU alone achieved a good or excellent outcome in 45–78% of patients. Only one patient was reported as a complete non-responder. Injections with 5-FU and TAC resulted in 50–96% good or excellent outcomes, and neither non-responders nor recurrence were reported. 5-FU was reported as less, as well as more, effective in direct comparison with TAC. Sadeghinia & Sadeghinia (10) who used TAC tattooing, an uncommon method of administration, showed better results with 5-FU than with TAC. Prabhu et al. (11) showed better volume reduction with TAC, also more pain reduction and less adverse events, although the last 2 were not significant. Saha & Mukhopadhyay (12) showed comparable size reduction and recurrence rates, but less pain reduction and more adverse events in the 5-FU group. The combination of 5-FU and TAC (TAC:5-FU) proved more effective than 5-FU alone (13). Also, TAC:5-FU was more or equally effective and resulted in fewer adverse events than TAC alone (8, 14, 15). Most authors reported no recurrence of disease, while others reported recurrence in no less than 25–47% of patients (Table I). Excision with 5-FU achieves a good result, with recurrence rates between 4–19% (16–20). Keloid-free outcome after excision was 43% and after excision with 5-FU 75%, when TAC:5-FU was used after excision keloids were reduced by 92% (16–18) (Table II). A correlation between duration of

Table II. *Overview of studies using 5-fluorouracil in combination with surgical excision in keloid treatment*

Reference (year)	Treatment used	Patients/ keloids in this group, *n*	Evidence level[a]	Definition keloid	Measurement method	Conc. injections (mg/ml)	Max dose/ injection (mg)	Time of 1st injection post surgery, weeks	Injections, *n*	Injection interval, weeks	Follow-up from surgery, weeks	Outcome	Recurrence, %
Uppal et al. (2001) (19)	excision+5-FU	6 P	2b	R	NR	50	NR	0	NI	–	26	50% fair, 50% good improvement[e]	NR
	RCT control excision	61 P				–	–	–	–	–	26	87% poor, 13% fair improvement[e]	NR
Davison et al. (2009) (18)	excision+TAC:5-FU	24 K	2b	NR	NR	10:37.5	NR	0	4	2	26–313	On average excellent flattening (92%)[b]	NR
	RCT control excision+TAC	26 K				40	NR	0	4	2	26–313	On average good flattening (73%)[b]	NR
Haurani et al. (2009) (24)	excision+5-FU	32 P	2b	R	R	50	50	2	10	4	100	10% no, 27% fair/good, 63% excellent improvement[e]	19
Hatamipour et al. (2010) (16)	excision+5-FU+SS	25 P	2b	R	NR	50	50	1	5	1/2/4[d]	100	21% fair/good, 75% excellent improvement[e]	4
	RCT control excision + SS	25 P				–	–	–	–	–	100	35% fair/good, 43% excellent improvement[e]	22
Khare & Patil (2012) (20)	excision+5-FU	28 P	4	NR	NR	NR	150	0	1	–	>52	96% excellent result	4
Wilson (2013) (17)	excision+5-FU:Botox	80 P	4	R	NR	50:50IE	500	0	1	–	>52	16% no–poor, 84% good–excellent improvement[e]	4

Besides excision and intralesional 5-FU, a maximum of one other treatment modality has been used when indicated (triamcinolone acetonide (TAC), botulinum toxin, silicone sheets).
[a]Level of evidence rated by Centre for Evidence Based Medicine criteria, March 2009 (www.cebm.net). [b]No 0%, poor 1–25%, fair 26–50%, good 51–75%, excellent 76–100% keloid flattening. [c]No 0%, poor 1–25%, fair 26–50%, good 51–75%, excellent 76–100% keloid improvement. [d]Injections were at week 1, 2, 4, 8, 12.
Botox: botulinum toxin; K: keloids; NI: no injection (5-FU soaked sponge pledged intraoperative for 5 min); NR: not reported; P: patients; R: reported; SS: silicone sheets; RCT: randomized controlled trial.

keloids and treatment response, where younger keloids respond favourably, was found in 2 studies (21, 22), while others did not find this correlation (23).

5-FU treatment protocols

Fitzpatrick (9) tried different injection intervals and recommended starting with once-weekly injections, advice which many others followed (8, 11–13, 15, 16, 21–23). Others used 2- or 4-week intervals (10, 14, 18, 24, 25) or only once around surgery (17, 19, 20). The outcomes do not indicate a preference for a specific injection-interval. Where serial injections were used, 6 studies used 3–6 injections and 8 used 8–16.

None of the authors reported serious side-effects. Six studies found no side-effects at all (8, 10, 15, 16, 24, 25). Reported were purpura (20–40%), ulceration (1–65%), and transient hyperpigmentation (90%) (9, 11, 12, 14, 21–23). In 6 surgical studies complications of necrosis, wide scars (14%) and dehiscence (1–18%) were rarely found (17, 20). No systemic reactions were found after local injection (8–10, 12, 16, 21, 22, 24).

Without exception the manufacturer concentration of 50 mg/ml was used when 5-FU was used alone. Mild side-effects, due to local toxicity advise against using higher concentrations. Lower concentrations would require more volume for the same active dose, which increases pain on injection. In combination therapy, the TAC concentrations were very low (TAC:5-FU of 1:45 mg/ml or 4:45 mg/ml); only Davison et al. (18) tested TAC:5-FU in 10:37.5 mg/ml and noticed more side-effects than they had with TAC (23% vs. 15%, not significant).

DISCUSSION

This systematic review indicates that the combination of TAC:5-FU may be more effective than TAC alone in keloid treatment (level C evidence). After keloid excision, 5-FU reduces recurrence rates to 4–19%, both on its own and in combination with TAC.

Our literature search resulted in a remarkably high number of reviews (126 of 284 papers), most of which were mainly on scar or pathological scar treatment, and mentioned 5-FU only in passing. Due to the unambiguity of our search terms the risk of missing relevant publications was minimal, as reflected by the absence of additional includes in our reference check. There were, however, several papers in the Asian literature that were not in English or that we could not retrieve.

The level of evidence was poor, there were 10 RCTs (8, 10–16, 18, 19), some of which were unfortunately executed very poorly, 4 prospective single-arm trials (17, 18, 20, 25), 4 case series and an expert opinion (9, 21–24). The problems included a lack of definitions, suboptimal study designs and follow-up periods. The studies we found on the novel treatment 5-FU were small, wherefore the good efficacy reported at first is probably influenced by publication bias. More recent studies on 5-FU are less positive in their results (11, 12).

Due to the large heterogeneity between studies, a meta-analysis could not be performed. This is reflected in the lack of a good definition of keloids in 11 of the 18 articles. Here less severe hypertrophic scars could be included that positively influence the results (8, 14, 26–28). Similarly, outcome measurement technique was poorly described, and outcomes were classified in wide ranges ("good result" or "improvement 75–100%"). This forced us to do the same (12–25).

With intralesional 5-FU a good to excellent response was found in 45–79% of treated cases, and even up to 96% if TAC was added. It is unclear what caused the lowest response (45%) (22): it cannot be explained by dose, follow-up time, or number of injections. The wide range of effectiveness we found is recognized from research on intralesional corticosteroid use alone, where a 50–100% response is reported (4). A favourable response was seen in small and previous untreated lesions; this phenomenon is also known in other keloid treatments (1, 21, 22).

Recently the synergetic effect of TAC and 5-FU was proven in an *in vitro* study on keloid fibroblasts (29). Although the evidence is weak, TAC:5-FU is more effective than 5-FU alone and seems to have advantages over TAC alone. The beneficial results of TAC:5-FU compared with TAC are, however, highly dependent on the dose and injection scheme of TAC and TAC:5-FU. Khan et al. (15) used low concentrations of TAC, which are less effective in keloid treatment, and weekly injections, that due to the long duration of action of TAC might cause more atrophy. For TAC:5-FU there is very little evidence on the efficacy and safety of TAC concentrations greater than 4 mg/ml, therefore we recommend the most frequently used and investigated concentration of 4:45 mg/ml TAC:5-FU. There is insufficient evidence for a statement on the maximum allowed dose in total or per scar-surface area.

Weekly injections are mostly used; therefore most evidence is based on this injection interval. Although Fitzpatrick (19) states that longer intervals are less effective, this is not reflected by the studies we present. However, none of the studies directly compared different injection intervals. Also, the number of injections varied widely between studies (1–16) without a clear correlation with the outcome. When more injections were allowed clinical evaluation was used to determine the need for additional treatment.

Even though keloid recurrence is a major problem, some studies fail to report recurrence rates. Others have less than a year follow-up period, which is too short to draw a valid conclusion on recurrence rates (8, 10, 11, 14, 15, 18, 19, 21, 23, 30). Five studies (follow-up 13–52 weeks) remarkably found no recurrence (13–15, 21, 23). Higher recurrence rates of 25–47% were found

after 52 weeks or longer follow-up (12, 22, 25). The low recurrence risks found can be partly explained by the inclusion criteria or study designs, many studies selected patients with more favourably characteristics than the keloid-patient group that is usual in most clinics.

Based on this systematic review, we recommend 4:45 mg/ml TAC:5-FU combination therapy, injected intralesionally, until a satisfactory response is reached. It is likely that approximately 8 injections are needed. However, in order to formulate valid clinical guidelines on how to use TAC:5-FU in keloid treatment, more high-level clinical evidence is needed. This will help to establish preferred doses and injection schedules.

ACKNOWLEDGEMENT

This work was supported by the NutsOhra Foundation.

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