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REVIEW

A Narrative Review of Amniotic Membrane Transplantation in Ocular Surface Repair: Unveiling the Immunoregulatory Pathways for Timely Intervention

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ABSTRACT

This narrative review explores the pathophysiology of ocular surface inflammation and highlights the therapeutic potential of patch amniotic membrane transplantation (patch-AMT) in ocular surface repair. Disruptions in ocular surface homeostasis caused by trauma, disease, or immune dysregulation trigger an inflammatory cascade that, if unresolved, can impair epithelial healing, lead to fibrosis, corneal haze, and vision loss. Patch-AMT provides a biological intervention with epitheliotropic, anti-inflammatory, anti-fibrotic, anti-angiogenic, and neuroprotective effects that support wound healing, regulate inflammation, and reduce pain. The review examines patch-AMT's role in acute conditions (chemical burns, Stevens-Johnson Syndrome) and chronic disease (persistent epithelial defects, dry eye disease), focusing on its ability to entrap immune cells, regulate cytokine signaling, and prevent fibrotic remodeling while releasing trophic proteins. Additionally, this review explores how preservation methods, application orientation, and intervention timing influences patch-AMT's efficacy. Recent advancements in non-surgical application methods have expanded accessibility, enabling earlier intervention and outpatient use. However, variability in clinical protocols emphasize the need for standardized guidelines. The review concludes by highlighting the need for further research to refine treatment timing, optimize repeat application strategies, and evaluate cost-effectiveness. While patch-AMT remains underutilized, growing evidence underscores its potential to improve clinical outcomes, particularly when applied early in disease progression.

Keywords: Inflammation; Cornea; Ocular surface disease; Patch-AMT

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Key Summary Points

Immunoregulatory role of patch-AMT. Patch amniotic membrane transplantation (patch-AMT) provides key immunoregulatory benefits, including reduction of inflammation, promotion of epithelial healing, and prevention of stromal fibrosis in ocular surface conditions

Early intervention advantage. Early application of patch-AMT in acute ocular surface injuries and diseases, such as burns or Stevens-Johnson Syndrome, mitigates inflammation escalation, accelerates recovery, and improves visual outcomes

Advancements in accessibility. Developments in sutureless AMT and outpatient-friendly technologies have expanded access to treatment across a broader spectrum of ocular surface diseases

Influence of Preservation methods and orientation. Preservation method, application orientation, and treatment duration significantly influence therapeutic efficacy

INTRODUCTION

Ocular surface homeostasis relies on epithelial integrity, immune regulation, tear film stability, neurovascular function, and normal blinking [1]. Disruptions, whether from trauma, infection, or immune dysregulation, can trigger an inflammatory cascade [2], leading to stromal fibrosis, corneal haze (myofibroblast activation and extracellular matrix deposition), and vision loss (Fig. 1) [3–7].

Amniotic membrane transplantation (AMT) is a biologically active therapy with immunoregulatory, anti-inflammatory [4], anti-fibrotic [6], epitheliotropic [8–10], anti-angiogenic, and neuroprotective properties [11, 12]. These combined effects, along with its barrier function, allow AMT to modulate inflammation, promote wound healing, and prevent fibrosis [10, 13–16].

Depending on disease severity and therapeutic objectives, AMT can be applied in different modes [15, 17, 18]. Traditionally, AMT has been used for wound healing and under complex reconstruction conditions [19, 20], but patch-AMT is increasingly recognized for its immunoregulatory role in acute and chronic ocular surface diseases, including chemical burns, Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), persistent epithelial defects (PED), dry eye disease (DED) and as an adjunct therapy in the management of infectious keratitis [17, 21–23].

Despite its well-documented benefits, patch-AMT remains underutilized [24]. This is due to inconsistencies in application techniques, preservation methods, and logistical constraints (Table 1) [2, 17, 24]. However, recent advances in non-surgical sutureless patch-AMT application have improved accessibility and reduced costs, facilitating earlier intervention and outpatient use [19, 20, 25, 26].

This narrative review focuses on the pathophysiology of ocular surface inflammation and the immunoregulatory mechanism of patch-AMT. By synthesizing evidence from preclinical and clinical studies, the review highlights the clinical relevance of patch-AMT application, different preservation methods, application techniques, and the importance of intervention timing in inflammation control.

This article is a narrative review of previously published studies and does not involve any new studies with human participants or animals performed by the authors. As such, ethical approval was not required.

PATHOPHYSIOLOGY OF OCULAR SURFACE INFLAMMATION

Disruption to ocular surface homeostasis initiates a multiphase inflammatory cascade that, if unresolved, can impair epithelial healing, induce fibrosis and opacity, and lead to vision loss (Fig. 1) [3–7].

Acute Inflammation Basement Membrane Breakdown

Epithelial injury or stress triggers pro-inflammatory cytokine (interleukin [IL]-6 [IL-6], tumor necrosis factor-alpha [TNF-α], and IL-1 beta [IL-1β]) release (Fig. 1b) [27–29], which together with chemokines (monocyte chemoattractant protein 1 [MCP-1] and IL-8), lead to the recruitment of polymorphonuclear neutrophils (PMNs) [27–29]. PMNs release reactive oxygen species (ROS) and matrix metalloproteinase-9 (MMP-9), a key enzyme in tissue remodeling, which degrades the basement membrane (BM) and extracellular matrix (ECM), delaying epithelial closure and intensifying inflammation [30–33].

BM breakdown exposes the stroma to inflammatory mediators (Fig. 1d), particularly IL-1α and TNF-α, which drives keratocyte apoptosis and immune cell infiltration [30, 34, 35]. Since keratocytes play an important role in regulating corneal transparency [36, 37], their loss initiates stromal disorganization, ECM remodeling, and progressive fibrosis (Fig. 1e) [36–38].

Fibrosis and Corneal Haze Formation

Persistent inflammation activates fibroblasts, which transform into myofibroblasts via the key fibrogenic cytokine, transforming growth factor-beta (TGF-β) [37, 39]. Myofibroblasts deposit excessive ECM (collagen I and III), causing corneal haze and scarring (Fig. 1e, f). PMNs exacerbate inflammation through excessive pro-inflammatory cytokine release, oxidative stress, proteolytic activity (e.g., MMP-9), further intensifying keratocyte apoptosis and ECM remodeling [40, 41]. Without effective immune resolution, prolonged myofibroblast activity causes irreversible fibrosis [3, 40, 42].

Chronic Inflammation and Progressive Damage

Failure to resolve acute inflammation leads to chronic macrophage infiltration, lymphocyte activation, and sustained cytokine signaling (Fig. 1F) [37]. Chronic inflammation disrupts epithelial healing and depletes limbal stem cells, causing progressive corneal damage and conjunctivalization.

Chronicity and Neurogenic Inflammation

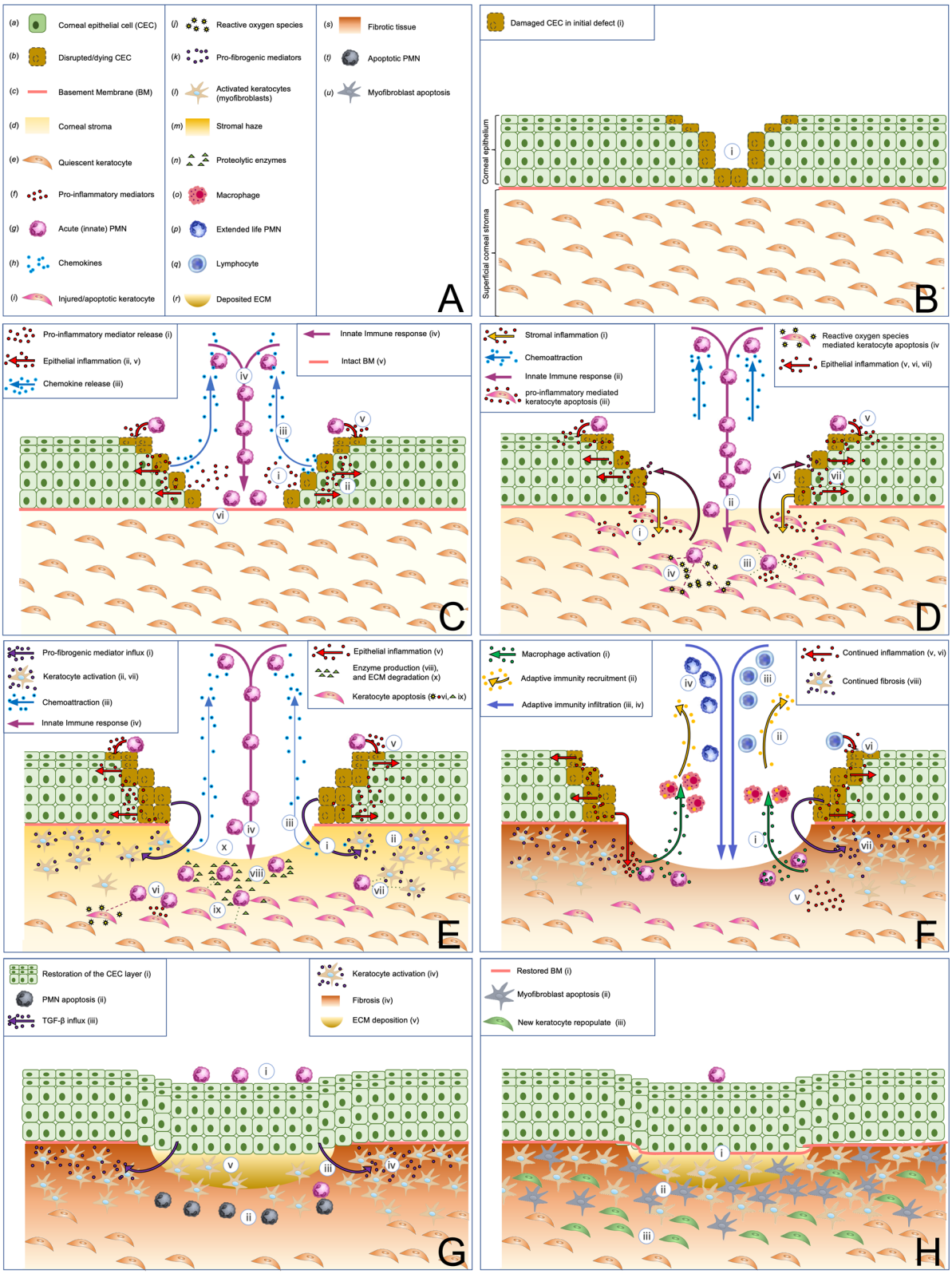
Corneal nerves regulate immune homeostasis, but inflammation-associated nerve injury triggers immune dysregulation, releasing neuropeptide (substance P, calcitonin gene-related peptide [CGRP]), amplifying inflammation, and contributing to persistent epithelial instability, pain, and stromal fibrosis [43–45].

CLINICAL SIGNIFICANCE OF POOR IMMUNOREGULATION

Uncontrolled ocular surface inflammation leads to persistent tissue damage, delayed epithelial healing, scarring, and long-term vision impairment [37, 46, 47]. Poor immunoregulation manifests in PEDs, corneal haze, limbal stem cell deficiency (LSCD), and corneal neovascularization, all of which contribute to ocular surface instability and progressive visual loss.

Post-Refractive Surgery Corneal Haze and Stromal Fibrosis

Excimer laser-based surface ablation (ELSA), including photorefractive keratectomy (PRK) and laser-assisted subepithelial keratectomy (LASEK), induces controlled epithelial injury involving immune-mediated wound healing [48, 49]. Although epithelial closure typically occurs within 5 days, PMN infiltration and prolonged myofibroblast activity contribute to excessive ECM remodeling, leading to corneal haze [50, 51]. TGF-β signaling remains active until BM regeneration is complete (Fig. 1h) [37, 52], sustaining myofibroblast activation, fibrotic changes, and corneal haze [38, 39, 52, 53]. Early immune modulation is therefore critical to minimizing post-surgical fibrosis and ensuring optimal visual recovery.


(a) Corneal epithelial cell (CEC)
(b) Disrupted/dying CEC
(c) Basement Membrane (BM)
(d) Corneal stroma
(e) Quiescent keratocyte
(f) Pro-inflammatory mediators
(g) Acute (innate) PMN
(h) Chemokines
(i) Injured/apoptotic keratocyte
(j) Reactive oxygen species
(k) Pro-fibrogenic mediators
(l) Activated keratocytes (myofibroblasts)
(m) Stromal haze
(n) Proteolytic enzymes
(o) Macrophage
(p) Extended life PMN
(q) Lymphocyte
(r) Deposited ECM
(s) Fibrotic tissue
(t) Apoptotic PMN
(u) Myofibroblast apoptosis
A
Damaged CEC in initial defect (i)
Corneal epithelium
Superficial corneal stroma
B
Pro-inflammatory mediator release (i)
Epithelial inflammation (ii, v)
Chemokine release (iii)
Innate Immune response (iv)
Intact BM (v)
C
Stromal inflammation (i)
Chemoattraction
Innate Immune response (ii)
pro-inflammatory mediated keratocyte apoptosis (iii)
Reactive oxygen species mediated keratocyte apoptosis (iv
Epithelial inflammation (v, vi, vii)
D
Pro-fibrogenic mediator influx (i)
Keratocyte activation (ii, vii)
Chemoattraction (iii)
Innate Immune response (iv)
Epithelial inflammation (v)
Enzyme production (viii), and ECM degradation (x)
Keratocyte apoptosis (vi, ix)
E
Macrophage activation (i)
Adaptive immunity recruitment (ii)
Adaptive immunity infiltration (iii, iv)
Continued inflammation (v, vi)
Continued fibrosis (viii)
F
Restoration of the CEC layer (i)
PMN apoptosis (ii)
TGF-β influx (iii)
Keratocyte activation (iv)
Fibrosis (iv)
ECM deposition (v)
G
Restored BM (i)
Myofibroblast apoptosis (ii)
New keratocyte repopulate (iii)
H

◂**Fig. 1** Pathophysiology of corneal inflammation following epithelial damage. This figure outlines the sequential stages of corneal inflammation and repair following epithelial damage, emphasizing key inflammatory and reparative mechanisms. **A** Color-coded key summarizing the stages of inflammation. **B** Initial epithelial insult. **C** Acute inflammation in the first 24 h and pro-inflammatory cytokines release (*i*) perpetuates tissue damage and inflammation (*ii*) and triggers innate immunity (*iii*). PMNs are recruited (*iv*) and release pro-inflammatory cytokines and proteolytic enzymes that exacerbate epithelial (*ii*) and stromal damage. An intact BM (*vi*) prevents inflammatory infiltration into the stroma (*vi*). **D** Compromised BM enables the penetration of inflammatory cytokines (*i*) and cells (*ii*), leading to keratocyte apoptosis. Infiltrated PMNs release pro-inflammatory cytokines (*iii*, *viii*) and free radicals (*iv*), which in turn impedes healing (*v*) and drives keratocyte apoptosis (*vi*) [3, 40, 42]. **E** TGF-β influx during the first 48 h actives fibrosis (*i*), myofibroblast activity associated with haze, and scarring (*ii*, *iii*). Continued inflammation (*iv*) impedes epithelial healing (*v*) [3], promoting further keratocyte apoptosis and PMN infiltration (*vi*, *vii*) [7, 42]. Stromal degradation (*ix*, *x*) progresses. **F** PMNs are typically short-lived, undergoing apoptosis within 3–5 days, which defines the acute phase of ocular surface damage [37] but transitions to chronic inflammation from day 7 triggering macrophage recruitment (*i*), adaptive immune response (*ii*), and lymphocyte and extended life PMN infiltration (*iii*, *iv*) [2]. This exacerbates tissue damage (*v*, *vi*, *vii*). **G** Healing phase: epithelial closure reduces inflammation by preventing inflammatory cell infiltration (*i*), and PMN apoptosis occurs (*ii*), but fibrosis continues (*iii*, *iv*). **H** BM restoration quenches TGF-β influx (*i*), triggers IL-1-mediated myofibroblast apoptosis (*ii*) [37, 120], enabling keratocyte renewal and ECM remodeling (*iii*) [120]. *BM* Basement membrane, *CEC* corneal epithelial cell, *ECM* extracellular matrix, *IL* interleukin, *PMNs* polymorphonuclear leukocytes, *TGF-β* tumor growth factor beta

Persistent Epithelial Defects and Corneal Scarring

Persistent epithelial defects result from impaired epithelial migration and attachment, often driven by excessive MMP-9 activity and cytokine dysregulation [31–33]. Failure to re-epithelialize exposes the corneal stroma to chronic inflammation, leading to stromal degradation and permanent corneal opacification [37, 39].

Corneal Melting and Perforation

Excessive proteolytic enzyme activity, particularly from MMPs and neutrophil elastase, can degrade the corneal stroma, causing thinning and perforation [8, 21, 23, 54–57]. In these cases, urgent intervention with AMT, or keratoplasty is required to preserve globe integrity. Early immunomodulation remains essential to stabilizing the ocular surface and preventing further stromal loss.

Severe Inflammatory Conditions: Chemical Burns and SJS

In chemical burns, substantial cytokine release (IL-1β, TNF-α, IL-6) and oxidative stress induces extensive epithelial destruction, chronic pain, fibrosis, and LSCD [2, 58]. Delayed or inadequate treatment leads to corneal conjunctivalization, scarring, and vascularization, all of which further impair visual outcomes.

In SJS/TEN, autoimmune-mediated epithelial apoptosis and persistent inflammation lead to severe DED, corneal keratinization, and progressive ocular surface failure [59]. Uncontrolled immune activation exacerbates tissue loss, necessitating early aggressive therapeutic intervention to mitigate irreversible damage [60].

While conventional anti-inflammatory treatments suppress immune activation, they do not actively promote epithelial healing or prevent fibrosis [61]. AMT, by contrast, directly modulates inflammation while supporting corneal repair. In section The Immunoregulatory Benefits of AMT, we explore the immunoregulatory mechanisms and therapeutic potential of AMT in ocular surface disease.

THE IMMUNOREGULATORY BENEFITS OF AMT

Amniotic membrane is an immune-privileged tissue that plays a pivotal role in fetal development by protecting against maternal immune rejection, exerting direct immunoregulatory effects that counteract inflammation-driven

Table 1 Summary of clinical papers reporting anti-inflammatory benefit of patch-amniotic membrane transplantation

Author (et al.)	Year of publication	Mode[a]	Orientation (down)[b]	AMT duration (days)[c]	Amniotic membrane type[d]	Environment[d]	Clinical indication[e]	Disease phase[f]	Days to AMT[f]	Study type[g]	*N*= n=)h	Evidenc[hi]
Refractive surgery												
Lee [91]	2004	P	Stroma	Healed	CPAM	S	ELSA	Acute	0	CCS	152 (94)	Haze
Vlasov [93]	2016	P	Stroma	7	PROKERA®	C	ELSA	Acute	0	CCS	40 (20)	Haze
Cox [94]	2020	P	Stroma	7	PROKERA®	C	ELSA	Acute	0	CCS	78 (39)	Haze
Ocular burns												
Arora [112]	2005	P	Stroma	–	Fresh	S	Chemical burns	Acute	< 21**	NCS	15 (15)	O
Tamhane [121]	2005	P	Stroma	7–18	CPAM	S	Burns	Acute	< 21**	RT	44 (24)	Ci
Prabhasawat [122]	2007	P	Stroma	9.8 (4–21)	CPAM	S	Burns	Acute	< 5	NCS	21 (21)	O
Kheirkhah [89]	2008	P	Stroma	3.7 × 3	Prokera®	C	Burns	Acute	< 8*	CS	5 (5)	IM
Tandon [19]	2011	P	Stroma	–	CPAM	S	Burns	Acute	< 2	RT	100 (50)	O
Liu [84]	2012	P	Stroma	7–9	CPAM	S	Burns	Acute	< 7*	NCS	30 (30)	IM
Sharma [20]	2016	P	Stroma	21	CPAM	S	Burns	Acute	< 7*	RT	51 (15)	Ci
Eslani [123]	2019	P	Stroma	–	CPAM	S	Severe (Grade IV) burns	Acute	< 7	TR	60 (30)	Ci
Dua [2]	2020	P	AEC	7	Omnigen	S	Burns	Acute				-
Mehta (90)	2021	P	AEC	–	Omnigen	C	Severe (Grade IV) Burns	Acute	–	CS	11 (17)	O

Table 1 continued

Author (et al.)	Year of publication	Mode[a]	Orientation (down)[b]	AMT duration (days)[c]	Amniotic membrane type[d]	Environment[d]	Clinical indication[e]	Disease phase[f]	Days to AMT[f]	Study type[g]	*N*= n=)h	Evidenc[hi]
Lotfy [25]	2023	P	AEC	7	Omnigen	C	Severe (Grade IV) Burns	Acute	2	CS	23 (28)	O
Meller [8]	2000	P	Both		CPAM	S	Thermal burns	Chronic	< 15	NCS	13 (13)	O
Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis												
Di Pascuale [109]	2005	P	–	< 9	CPAM	S	SJS	Acute	6	RC	38 (1)	O
Kobayashi [124]	2006	P	Stroma	Healed	CPAM	S	SJS	Acute	5	CA	1 (1)	O
Shammas [119]	2010	P	Stroma	Various	Prokera	S/C	SJS/TEN	Acute	~ 1	CS	12 (12)	O
Sharma [92]	2016	P	Stroma	–	CPAM	S	SJS	Acute	7–14**	RT	50 (25)	O
Ma [125]	2016	P	Stroma	7.5 ± 2.1	CPAM	S	SJS	Acute	–	CS	9 (9)	-
Shanbhag [110]	2019	P	Stroma	6–7	CPAM	S	SJS	Acute	< 4	CS	8 (8)	Haze
Epithelial defects/ulcers												
Tseng [126]	1998	P	AEC	–	CPAM	S	LSCD (mixed aetiology)	Chronic	LT	CC	26 (10)	O
Chen [127]	2000	S	AEC	–	CPAM	S	Neurotrophic ulcers	Chronic	PS	RS	16 (16)	O
Hanavar [128]	2000	P	Stroma	Healed	CPAM	S	SJS (LSCD)	Chronic	–	NC	10 (10)	O

Table 1 continued

Author (et al.)	Year of publication	Mode[a]	Orientation (down)[b]	AMT duration (days)[c]	Amniotic membrane type[d]	Environment[d]	Clinical indication[e]	Disease phase[f]	Days to AMT[f]	Study type[g]	*N*= n=)h	Evidenc[hi]
Shimmura [4]	2001	P	Stroma	7	CPAM (as)	S	PED (mixed etiology)	Chronic	> 14	NCS	20 (20)	IM
Dogru [129]	2003	S	AEC	–	CPAM	S	Corneal ulcers	Chronic	> 60	NCS	10 (10)	O
Maharajan [106]	2007	P	AEC	10–14	CPAM	S	Various	Chronic	–	CS	74 (74)	O
Maqsood [95]	2021	P	AEC	25	Omnigen	C	PED	Chronic	22 ± 12	CS	93 (106)	O
Maqsood [96]	2024	P	AEC	24.0 ± 14.1	Omnigen	C	PED	Chronic	25.1 ± 25.2	NCS	46 (46)	Ci
Ho [115]	2023	P	AEC	22 ± 26.5	Omnigen	C	PED	Chronic	27	CS	17	D
Infectious keratitis												
Kim [130]	2001	P	AEC	3	CPAM	S	Infection corneal ulcers	Acute	~ 3	NCS	21(21)	O
Chen [131]	2006	G	Stroma	–	CPAM	S	Fungal keratitis	Acute	> 7**	NCS	23(23)	O
Tabatabaei [23]	2017	G	Stroma	–	DNS	S	Bacterial keratitis	Acute	2–5	RT	100(49)	Ci
Dry eye disease												
John [11]	2017	P	Stroma	3.4 ± 0.7	PROKERA®	C	DED	Chronic	–	RT	20	D
McDonald [113]	2018	P	Stroma	5.4 ± 2.8 (2–11)	PROKERA®	C	DED	Chronic	–	CS	97(97)	D

Table 1 continued

Author (et al.)	Year of publication	Mode[a]	Orientation (down)[b]	AMT duration (days)[c]	Amniotic membrane type[d]	Environment[d]	Clinical indication[e]	Disease phase[f]	Days to AMT[f]	Study type[g]	*N*= n=)h	Evidenc[hi]
Travé-Huarte [132]	2024	P	AEC	8.1 ± 2.7	Omnigen	C	DED	Chronic	–	RT	35 (70)	Ci
Travé-Huarte [12]	2024	P	AEC	–	Omnigen	C	DED	Chronic	–	RT	160 (80)	D
Other												
Solomon [133]	2002	S	Stroma	< 14	CPAM	S	Perforation	Chronic	–	NCS	34(34)	O

This table presents clinical evidence evaluating the anti-inflammatory effects of patch-amniotic membrane transplantation (AMT). It also provides a structured overview of AMT applications, linking therapeutic strategies to clinical outcomes for ocular surface repair

[a]Modes of AMT application, namely, patch (P), graft (G), and sandwich (S)

[b]The orientation of the amnion—amniotic epithelial cell (AEC) side or stromal side—facing the defect is specified. Dash indicates missing data

[c]AMT duration. Dash indicates missing data; number in brackets indicate range

[d]The type of amniotic membrane used (e.g., cryopreserved [CPAM], self-retained cryopreserved [Prokera], low temperature vacuum-evaporation dehydrated [Omnigen], fresh, or did not say [DNS]) and application settings (surgical [S] vs. non-surgical [C])

[e]DED, Dry eye disease; ELSA, Excimer laser-based surface ablation; LSCD, limbal stem cell deficiency; PED, persistent epithelial defects; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis

[f]Conditions treated are classified as acute, chronic, borderline acute (*), or sub-chronic (**). Dash indicates missing data

[g]Study design/type: NCS, prospective, noncomparative, interventional case series; CCS, prospective, comparative, interventional case series; RT, retrospective case series

[h]N (AMT): Number of treated eyes (and AMT-treated Eyes)

[i]Evidence of anti-inflammatory benefits supported by: clinical data (D), in vitro inflammatory cell analysis (IM), or observational findings, i.e., clinical observation but no data (O). Ci refers to no data but cited, and dash indicates missing data

tissue damage [14, 18]. Similarly, patch-AMT functions both as and biological barrier and a bioactive matrix capable of modulating immune response, suppressing pro-inflammatory cytokines and promoting epithelial healing, which are multifaceted mechanisms crucial in limiting corneal fibrosis and preventing long-term visual impairment (Fig. 2) [22, 62–65].

Entrapment and Apoptosis of Inflammatory Cells

One of the key immunoregulatory actions of patch-AMT is the sequestering of infiltrating inflammatory cells within its stromal matrix; patch-AMT physically entraps PMNs and macrophages, reducing their infiltration into the corneal stroma and limiting TGF-β- and MMP-driven fibrosis (Fig. 2b) [4, 66, 67]. Once trapped, these cells undergo apoptosis or functional modulation, facilitated by bioactive proteins [68–71], including Fas ligand (FasL), TNF-related apoptosis-inducing ligand (TRAIL), and macrophage inhibitory factor (MIF) [71–73].

FasL and MIF are key immunomodulatory proteins involved in maternal–fetal tolerance and immune privilege [63, 71, 74–76]. Their expression within amniotic membrane enhances its ability to suppress neutrophil and macrophage activation, thereby reducing cytokine-driven inflammation and stromal degradation. By controlling excessive immune cell infiltration, patch-AMT helps to preserve corneal stromal architecture and reduces excessive ECM remodeling, thereby limiting scarring and preventing disease progression.

Cytokine and Fibrosis Modulation

Patch-AMT exerts direct anti-inflammatory and anti-fibrotic effects by suppressing pro-inflammatory cytokines (IL-6 and TNF-α) while enhancing anti-inflammatory mediators such as IL-10 [77, 78]. Additionally, AMT modulates TGF-β signaling to inhibit myofibroblast differentiation, a key step in corneal haze formation and fibrotic scarring [39, 66]. These effects collectively reduce the risk of vision-compromising fibrosis following ocular surface injury.

Antioxidant and Anti-Proteinase Activity

Oxidative stress and excessive protease activity contribute significantly to corneal tissue breakdown and delayed epithelial healing. Patch-AMT absorbs ROS, reducing oxidative damage while simultaneously inhibiting MMP activity to protect the BM and ECM [40, 79–81] to enable expedited epithelial recovery.

Neuroprotective and Anti-Angiogenic Effects

Patch-AMT supports corneal nerve regeneration by promoting sensory nerve survival, which is crucial for ocular surface healing [11, 12, 64]. Additionally, patch-AMT suppresses vascular endothelial growth factor (VEGF)-driven neovascularization, which is critical in preventing LSCD progression and preserving visual function [64]. These neuroprotective effects further distinguish AMT from conventional anti-inflammatory treatments.

Given the ability of patch-AMT to modulate inflammation, control fibrosis, promote epithelial healing, and support nerve regeneration, this treatment represents a valuable intervention in ocular surface disease. Unlike pharmacologic treatments, which primarily suppress inflammation, AMT actively remodels the healing microenvironment to promote long-term tissue restoration.

In the following sections, we explore preclinical and clinical evidence supporting the immunoregulatory properties of AMT and assess how preservation methods, application orientation, and intervention timing influence its therapeutic efficacy.

PRECLINICAL EVIDENCE SUPPORTING AMT'S IMMUNOREGULATORY ROLE

Extensive preclinical studies have provided mechanistic insights into how AMT influences

inflammatory cell dynamics, epithelial healing, stromal preservation, and fibrosis prevention.

Reduction in PMN Infiltration and Stromal Haze

In a rabbit PRK model, Park et al. [40] demonstrated that a 24-h application of cryopreserved patch-AMT significantly reduced PMN infiltration and corneal haze, with effects persisting for up to 12 weeks ($p<0.001$). Similar studies have corroborated these findings, showing reduced inflammatory infiltration and enhanced stromal preservation [66, 82, 83]. In an Herpes simplex virus 1 (HSV-1) keratitis model, patch-AMT reduced inflammatory cell infiltration and also significantly reduced epithelial ulceration and stromal necrosis [67].

Entrapment and Apoptosis of Immune Cells

Chemical burn models have shown that patch-AMT actively modulates immune cell behavior by entrapping inflammatory cells and inducing

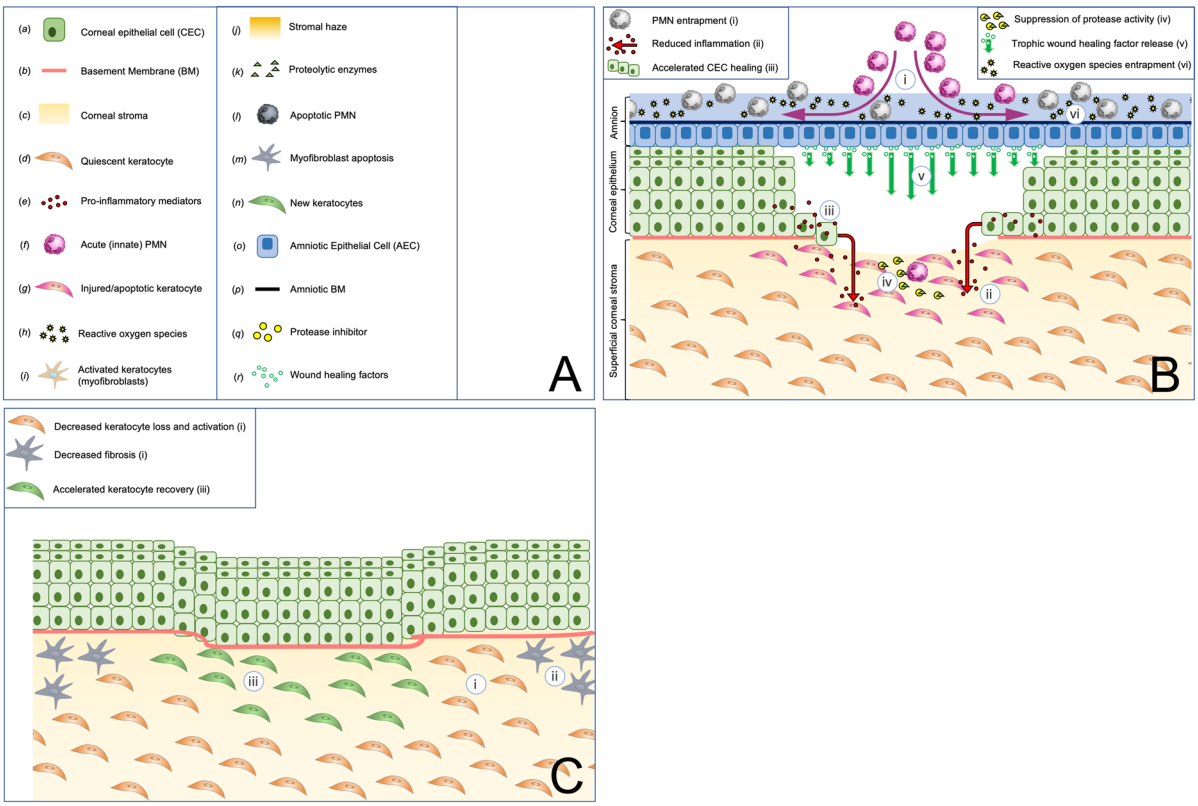


Fig. 2 The immunoregulatory role of the amnion in wound healing. This figure depicts the mechanisms by which patch-AMT) modulates inflammation and promotes wound healing. **A** Stages of amnion-mediated repair. **B** Depiction of how patch-AMT, applied post-injury, traps PMNs and inflammatory cells (*i*), thereby preventing stromal infiltration and keratocyte apoptosis (*ii*). The membrane's bioactive components aid epithelial healing (*iii*), inhibit proteinase and MMP activity (*iv*), and promote a favorable microenvironment for natural regeneration (*v*). **C** Benefits of patch-AMT, including reduced stromal damage (*i*), prevention of myofibroblast differentiation (*ii*), minimized haze, and restoration of stromal homeostasis (*iii*). Roman numerals align with labeled mechanisms in the figure, providing a detailed visualization of patch-AMT's multifaceted immunoregulatory effects. This figure emphasizes the importance of AMT in resolving inflammation, accelerating healing, and preserving corneal transparency. *AMT* Amniotic membrane transplantation, *MMP* Matrix metalloproteinase, *PMNs* polymorphonuclear leukocytes

apoptosis [81, 84]. Liu et al. [84] reported a significant reduction in CD147-positive PMNs and CD68+ macrophages following patch-AMT application, with a positive correlation with reduced MMP-9 activity and improved stromal preservation. Similarly, in HSV-1 keratitis models, patch-AMT induced apoptosis in trapped inflammatory cells, dampening the immune response and promoting faster epithelial recovery [68].

Macrophage Polarization and Fibrosis Prevention

AMT Plays an Active Immunoregulatory Role, Influencing Macrophage Behavior

Extracellular matrix heavy-chain hyaluronic acid (HC-HA) enhances the immunomodulatory profile of AMT by binding CD44 onto inflammatory cells, facilitating their entrapment and polarizing macrophages toward M2 pro-repair phenotypes [64, 68, 79, 85, 86]. This transition suppresses pro-inflammatory cytokine secretion (e.g., IL-6 and TNF-α), preventing excessive inflammation and fibrosis and preserving corneal architecture.

Prevention of Fibrosis and Corneal Haze

Woo et al. [83] reported that patch-AMT application post-PRK in rabbits significantly limited myofibroblast differentiation, thereby significantly reducing stromal haze and fibrosis. This highlights the potential of AMT to mitigate long-term fibrotic complications in controlled epithelial injuries.

Enhanced Epithelial Healing

The epitheliotropic properties of patch-AMT to accelerate epithelial closure by providing a protective scaffold that promotes epithelial migration reduces inflammatory cytokine activity, minimizing epithelial apoptosis. Choi et al. [82] observed that patch-AMT application reduced epithelial defect size by 30.5% ($p < 0.001$) within 3 days in the rabbit PRK model.

CLINICAL EVIDENCE SUPPORTING THE IMMUNOREGULATORY ROLE OF AMT

The immunoregulatory properties of patch-AMT have been extensively studied across various clinical indications, with the results demonstrating the ability of this treatment to modulate inflammation, accelerate epithelial healing, and prevent fibrosis

Reduction of Inflammatory Cell Infiltration and Modulation of Immune Responses

Advanced diagnostic tools, such as impression cytology tear biomarker analysis [87] and flow cytometry, have provided objective evidence of the immunoregulatory role of AMT. Ferrari et al. [88] established a correlation between ocular surface inflammatory grading scales (e.g., Efron and McMonnies scale) and quantitative measures of PMN infiltration, enabling the role of AMT in inflammation control to be further understood.

The findings from several clinical studies confirm that patch-AMT entraps and modulates inflammatory cells, preventing excessive immune infiltration into the corneal stroma and reducing proteolytic enzyme activity (Fig. 2). Shimmura et al. [4] evaluated patch-AMT in 12 patients with chronic PED with inflammation, demonstrating adaptive immune cell (CD14+ lymphocyte) entrapment. These authors reported that the results correlated with enhanced epithelial integrity following a 1-week stromal-side-down application. Kheirkhah et al. [89] reported that sequential sutureless applications of patch-AMT, with a mean duration of 3.7 days per application, significantly reduced the accumulation of inflammatory debris in moderate acute chemical burns; these authors also reported a correlation with accelerated epithelial healing in 80% of cases. Histological analysis of recovered patch-AMT confirmed inflammatory cell entrapment correlated to membrane cloudiness, which decreased with each application.

Liu et al. [84] demonstrated that surgically applied cryopreserved patch-AMT

(stromal-side-down, 7–9 days) entrapped inflammatory cells. Histopathological analysis of the retrieved AMT confirmed the presence of CD147-positive inflammatory cells, including CD15 + PMNs and CD68 + macrophages. The entrapment was associated with reduced MMP-9 activity and enhanced stromal preservation, reinforcing the role of AMT in immune modulation and proteolytic enzyme suppression. Furthermore, these authors reported that AMT's immunoregulatory effects were application dependent, noting that moderate disease achieved complete epithelial closure with a single AMT application, whereas severe burns required at least a second application to sustain inflammation control and achieve full healing, likely due to higher inflammatory cell burden [84]. Further studies also adopted repeat applications in severe cases to improve outcomes [25, 89, 90]. The ability to sequester immune cells within the amniotic matrix prevents infiltration into the corneal stroma, therefore mitigating immune-mediated tissue damage and proteolytic enzyme degradation.

Suppression of Fibrotic Pathways and Prevention of Corneal Haze

Post-injury and -surgery inflammation and persistent TGF-β activation drive myofibroblast differentiation and stromal fibrosis, leading to corneal haze. Patch-AMT actively suppresses cytokine activity and TGF-β signaling of fibroblast-to-myofibroblast transformation, preventing ECM deposition, which is a key mechanism underlying haze formation following refractive surgery and ocular surface injury (Table 1).

Lee et al. [91] studied 152 eyes (84 patients) undergoing LASEK and demonstrated that cryopreserved patch-AMT (stromal-side-down) reduced corneal haze scores (0.5 ± 0.2 vs. 2.5 ± 0.3 [controls]) and improved visual outcomes 4 weeks post-procedure. These findings aligned with preclinical results by Woo et al. [83], who demonstrated that patch-AMT not only acts as a physical barrier to inflammatory cells, but also serves as a bioactive reservoir that mitigates myofibroblast activity and promotes epithelial healing. Sharma et al. [92] reported that early patch-AMT application in acute SJS completely prevented corneal haze development (0/25) at 6 months, while corneal haze was still observed in 44% (11/25) of the medical therapy control group.

In non-surgical studies involving self-retained cryopreserved AMT (Prokera® corneal bandages; BioTissue, Miami, FL, USA), Vlasov et al. [93] and Cox et al. [94] observed variability in haze prevention and epithelial healing. These authors attributed this variability to potential mechanical trauma from the application ring-device rather than from the bioactivity of AMT.

Taken together, these findings confirm the immunomodulatory role of AMT in limiting myofibroblast activation and preventing the development of excessive stromal fibrosis.

Preservation of Corneal Integrity in Severe Acute Inflammatory States

Patch-AMT has been employed in high-risk ocular surface disease where excessive inflammation and proteolytic degradation contribute to severe tissue damage. While its efficacy is well-established in moderate injuries, its role in severe acute cases with extensive limbal ischemia (i.e., damage) remains limited, particularly in cases of chemical burns and SJS (Table 1).

In their study, Kheirkhah et al. [89] reported that sutureless patch-AMT in moderate (Grade I–III) acute chemical burns facilitated epithelial defect closure in all (5/5) cases undergoing treatment, with conjunctival defects healing within 8.2 days on average and corneal defects healing within 13.6 days on average. The study highlighted the role of patch-AMT in reducing acute inflammation and preserving limbal stem cells, potentially reducing long-term complications requiring surgical intervention.

Lui et al. [84] investigated early surgical patch-AMT (≤ 7 days) in chemical burns, reporting that moderate burns healed with a single application, while severe burns required a second application to sustain immunoregulatory benefits and better stabilize the ocular surface. However, epithelial healing remained compromised in cases with extensive limbal ischemia and stem

cell deficiency. These authors study highlighted that AMT reduced inflammation and promoted epithelial recovery in cases with residual limbal function, whereas in severe burns where limbal stem cell loss prevented epithelial regeneration, its role was to minimize pathology progression [84].

Tabatabaei et al. [23] demonstrated that early surgical patch-AMT, when used adjunctively in bacterial keratitis after initial antimicrobial therapy, improved visual outcomes and reduced corneal scarring compared to antibiotics alone. In this study, AMT was not intended for use in infection control but rather for modulating inflammation, suppressing proteolytic activity, and limiting neovascularization, thereby reducing the risk of perforation. Early application (within 2–5 days of antibiotic initiation) was associated with better structural and functional outcomes [23].

A randomized controlled trial by Sharma et al. [92] demonstrated that 'early' (7–14 days) surgically applied cryopreserved patch-AMT in severe SJS cases prevented LSCD, conjunctival congestion (an important indicator of active inflammation), and other ocular surface complications, whereas these remained prevalent in the medical therapy control group.

Promotion of Epithelial Healing and Modulation of Chronic Disease

In chronic inflammatory conditions, persistent low-grade inflammation impairs epithelial regeneration, contributing to ocular surface instability and recurrent ulceration. Patch-AMT has demonstrated significant benefits in reducing epithelial inflammation, stabilizing corneal homeostasis, and restoring regenerative capacity (Table 1).

Shimmura et al. [4] reported that a 1-week patch-AMT application in patients with PED resulted in marked reductions in epithelial inflammation. While existing fibrosis was not reversed, the study demonstrated AMT's role in stabilizing disease progression.

A recent randomized controlled trial by Travé-Huarte et al. [12] evaluated the efficacy of bilaterally applied dehydrated patch-AMT in refractory moderate-to-severe DED. At 6 months, these authors observed a significant 65% reduction in Ocular Surface Disease Index (OSDI) scores, decreased corneal dendritic cell density, and improved subbasal nerve plexus integrity. These results confirmed the long-term immunoregulatory and neuroprotective effects of AMT.

In chronic ocular surface diseases, repeated patch-AMT applications may help maintain functional efficacy. Unlike surgical AMT, non-surgical, in-clinic patch-AMT enables timely initial application and subsequent reapplications, supporting sustained immunomodulation and improved epithelial healing [95, 96].

Clinical evidence consistently demonstrates that patch-AMT modulates inflammation, prevents fibrosis, and promotes epithelial regeneration in both acute (chemical burns, SJS) and chronic (DED, PED) ocular surface diseases. By entrapping immune cells, regulating fibrosis, and enhancing epithelial healing, patch-AMT provides a biologically-driven approach to chronic ocular surface repair.

Key factors influencing the immunoregulatory efficacy of AMT, including preservation techniques, application orientation, and timing—to optimize clinical outcomes and therapeutic benefits, are discussed in section Key Factors Influencing the Immunoregulatory Benefits of Amnion .

KEY FACTORS INFLUENCING THE IMMUNOREGULATORY BENEFITS OF AMNION

The ability of patch-AMT to modulate inflammation, promote epithelial healing, and prevent fibrosis is influenced by its preservation method, application orientation, and intervention timing (Table 1).

Preservation Methods: Cryopreserved Versus Dehydrated AMT

Cryopreserved AMT is widely regarded as the benchmark for maintaining native ECM components, such as HC-HA/PTX3 [86]. However, damage caused by freezing and thawing may deplete the levels of soluble bioactive factors, including FasL, TRAIL, thrombospin-1, and TIMP metallopeptidase inhibitor 1 (TIMP-1), along with those of essential growth factors (epidermal growth factor [EGF], hepatocyte growth factor [HGF], TGF-β1, and TNF-α), all of which are crucial for inflammation resolution and epithelial regeneration [65, 77, 97–100].

Dehydrated amnion offers a number of advantages, including longer shelf-life, ease of use, and room temperature storage, making it more accessible for point-of-care application. However, traditional dehydration methods (heat and freeze-drying) may degrade ECM proteins and biomolecules [101–103], potentially diminishing therapeutic efficacy. Recent advancements in dehydration technologies have resulted in the improved preservation of immunoregulatory proteins and ECM integrity, enhancing AMT's therapeutic potential [22, 65].

Application Orientation: Epithelial versus Stromal Side Down

The orientation of the AMT during application affects its interaction with the ocular surface and immune system. The amnion has two distinct surfaces, namely, the epithelial (AEC) and stromal surface, each with unique bioactive properties. Results from preclinical studies suggest that orientation can modulate inflammatory cell entrapment, epithelial healing, and stromal remodeling [40, 81]. However, as highlighted in Table 1, no clinical consensus exists on the optimal orientation, highlighting the need for standardized protocols [17, 21].

AEC-Side-Down (stroma facing up)

This orientation (stroma facing up) maximizes inflammatory cell entrapment and apoptosis, (Fig. 2) [40, 77, 81], but the exposed stromal layer (spongy layer) may adhere to the lid margin, leading to potential problems such as AMT dislocation (personal communication, F. Figueiredo).

Stromal-Side-Down (AEC side Up)

This orientation functions as a physical barrier against inflammatory cell infiltration [40, 81], but may require more frequent re-applications in severe cases, such as chemical burns, to sustain anti-inflammatory effects [84, 89, 104]. Additionally, adherence to the exposed corneal stroma can delay epithelial closure [91, 105], contributing to haze persistence, as suggested by Wang et al. [66] in PRK models.

Further studies are needed to establish optimal orientation protocols for standardized application [84, 89].

Timing of Patch-AMT Intervention

In severe ocular surface disease, graft-AMT (inlay) has historically been reserved for later-stage application, following the resolution of acute inflammation. Maharajan et al. [106] reported that graft-AMT was more effective when applied after inflammation subsided, likely because it functions as a structural substrate supporting epithelial regrowth, which requires a stable microenvironment. However, patch-AMT serves a distinct role, acting earlier in the disease course by modulating inflammation, suppressing proteolytic activity, and preventing further tissue damage. While graft-AMT is best suited for structural repair, patch-AMT is ideally positioned for early intervention to limit inflammatory damage and preserve regenerative potential (Table 1).

In acute ocular injuries, such as chemical burns and SJS, 'early' surgical patch-AMT has traditionally been applied within 6–10 days (Table 1) [20, 92, 107–109]. However, increasing evidence suggests that intervention within < 6 days significantly reduces complications and improves visual outcomes, particularly in moderate burns and infectious keratitis [19, 23, 108, 110].

Despite its efficacy, logistical challenges (e.g., operating room availability, specialized expertise, and AMT supply) often contribute to delayed application [111]. Delayed intervention in acute conditions, such as chemical burns and SJS, increases the risk of LSCD, fibrosis, and scarring, leading to poorer long-term outcomes [107, 108, 112]. In cases of extensive limbal ischemia and conjunctival damage, AMT alone may not be sufficient to prevent LSCD [107, 108], necessitating subsequent interventions, such as limbal stem cell transplantation or tenoplasty. However, earlier patch-AMT application may help suppress ischemic inflammation, prevent further limbal damage, and reduce fibrosis and scarring, thereby preserving epithelial healing potential [84, 86, 89].

EXPANDING ACCESS TO EARLIER AMT INTERVENTION: ADVANTAGES OF NON-SURGICAL PATCH-AMT

While early surgical patch-AMT has shown promise, its role in severe injuries with extensive limbal ischemia remains uncertain. Ghosh et al. [107] reported that when applied within 5–10 days, Dua Grade > IV cases still developed LSCD, highlighting the need for additional interventions in these cases. However, other studies have suggested that earlier intervention within < 6 days can reduce the impact of Grade IV burns [108], supporting patch-AMT as an improved adjunctive therapy for earlier intervention in severe disease.

The development of non-surgical patch-AMT technologies has broadened accessibility by eliminating surgical delays, allowing for earlier treatment in both acute and chronic ocular diseases. Unlike surgical patch-AMT, which is typically a one-time intervention due to surgical costs, non-surgical patch-AMT can be reapplied as needed, sustaining its immunoregulatory and healing benefits [26, 95, 96]. This adaptability is particularly relevant in cases requiring ongoing inflammation control and epithelial regeneration.

Self-retained cryopreserved AMT (e.g., Prokera®; AmnioClip [DGFG, Hannover, Germany]) has been used in the management of epithelial defects and DED [11, 26, 89, 113]. However, its reliance on cold-chain logistics, potential patient discomfort, and variable treatment tolerance have limited widespread adoption [89, 93, 94, 104].

In contrast, sutureless dehydrated patch-AMT (e.g., AmbioDisc [Corza Medical, Westwood, MA, USA], Omnigen) offers greater practicality, allowing for both scheduled and emergency applications [65, 90, 95, 114]. Studies report that non-surgical dehydrated patch-AMT provides comparable, or superior, outcomes to sutureless cryopreserved patch-AMT [25, 90, 95, 96, 115].

A prospective study by Lotfy et al. [25] demonstrated that dehydrated patch-AMT applied within 48 h of acute chemical eye injuries resulted in complete healing within 1 month in all 23 eyes, including severe (Grade IV) cases, with 43% exhibiting severe limbal ischemia. Repeat applications in severe cases improved final outcomes and stability, although mild limbal ischemia (< 1/3 limbus) persisted in 13% (3 eyes). In refractory PED, complete epithelial closure rates of up to 94% have been reported within 25 days [95, 96, 115].

The flexibility of non-surgical patch-AMT, combined with its practicality and cost-effectiveness, makes it a viable option in both routine and urgent care settings where surgical patch-AMT may not be feasible [12]. While repeat applications may benefit moderate-to-severe acute disease, the role of repeat applications in severe limbal-conjunctival damage remains adjunctive rather than definitive. Repeat applications should be carefully tailored to individual cases, with factors such as wound stability, risk of mechanical trauma, and suitability for sutureless procedures taken into consideration. In cases of complete limbal stem cell failure, AMT plays a crucial role in stabilizing the ocular surface, preventing further degradation, and creating an environment conducive to subsequent stem cell transplantation for ocular surface restoration [25, 84, 89].

While early and repeated application of patch-AMT has the potential to improve the management of acute and chronic ocular surface diseases, the optimization of patch-AMT protocols,

including preservation methods, application orientation, and timing, is essential for maximizing therapeutic outcomes in ocular trauma and inflammatory disease management.

HEALTH ECONOMIC BENEFITS OF PATCH-AMT

Ocular surface diseases can impose a significant socioeconomic burden, with vision impairment affecting quality-adjusted life years (QALYs) and productivity at levels comparable to those of major chronic diseases like diabetes and cardiovascular disease [116–118].

The cost-effectiveness of patch-AMT lies in its ability to be applied early (≤ 6 days post-injury) [19, 23, 119] and non-surgically [89, 93, 94], thereby improving recovery and reducing the need for downstream invasive procedures and long-term vision impairment. Dehydrated, non-surgical patch-AMT further eliminates cold-chain storage and logistical barriers associated with traditional cryopreserved AMT. Its feasibility in outpatient, emergency, and unscheduled care settings facilitates earlier intervention, with potential benefits in accessibility and cost efficiency across different healthcare systems.

Studies have reported high epithelial healing rates following non-surgical patch-AMT, particularly in PED and acute chemical injuries [25, 90, 95, 96, 115]. While initial evidence supports the cost-effectiveness of patch-AMT compared to surgical alternatives, further research is needed to quantify its long-term impact on healthcare costs and resource utilization across different settings.

LIMITATIONS AND FUTURE DIRECTIONS FOR PATCH-AMT APPLICATIONS

Despite the therapeutic potential of patch-AMT, broader clinical adoption of patch-AMT is influenced by logistical, procedural, ethical, and regulatory challenges. Variability in preservation methods and application techniques may impact clinical outcomes [13, 106], although recent advancements, such as dehydrated amniotic membranes, have improved bioactivity consistency and accessibility [22, 65].

Standardizing application protocols and clinician training is critical for ensuring reproducible outcomes and improving the integration of patch-AMT into more routine care [12, 17, 22, 40, 89, 104]. Ethical concerns regarding donor consent, tissue traceability, and regulatory oversight have largely been addressed through strict adherence to international safety standards [22]. To date, no published cases of infection transmission have been reported despite widespread clinical use of AMT.

Future research should focus on refining personalized protocols for patch-AMT; comparing surgical versus non-surgical AMT for preventing LSCD, corneal haze, and long-term complications; optimizing application timing, duration, orientation, and repeat application criteria to maximize therapeutic efficacy; and assessing healthcare cost-effectiveness and standardizing application protocols across healthcare systems.

By addressing these challenges, patch-AMT could become an integral component of ocular surface disease management, expanding its role in both acute and chronic care settings.

CONCLUDING REMARKS

Ocular surface inflammation, if unregulated, disrupts corneal integrity, delays epithelial healing, and drives stromal fibrosis, ultimately leading to vision impairment. Conventional anti-inflammatory and wound-healing strategies often focus on symptom control rather than addressing the underlying immune dysregulation. Patch-AMT has emerged as a biologically driven therapeutic option that not only provides a protective scaffold but actively modulates the inflammatory response, prevents fibrosis, and promotes epithelial regeneration.

In this review, we have outlined the multifaceted immunoregulatory mechanisms of patch-AMT, including its ability to sequester

inflammatory cells, suppress pro-fibrotic pathways, and restore corneal homeostasis. Evidence from preclinical and clinical studies supports the efficacy of patch-AMT in acute inflammatory conditions such as chemical burns, SJS, and PED, as well as in chronic ocular surface diseases, including DED.

Despite the demonstrated clinical benefits of patch-ATM, broader and earlier adoption of this treatment has been hindered by logistical, procedural, and regulatory challenges, particularly regarding the standardization of preservation methods, application techniques, and treatment protocols. Recent advancements, including non-surgical, sutureless application techniques and room-temperature stable dehydrated AMT, have improved accessibility, allowing for earlier intervention and outpatient-based treatment. However, further research is needed to optimize treatment timing, refine indications for repeat applications, and establish comparative cost-effectiveness against conventional therapies.

Looking ahead, standardizing clinical protocols, ensuring consistent preservation techniques, and conducting comparative trials across different healthcare settings will be key to maximizing the therapeutic benefits of patch-AMT. The ability of patch-AMT to modulate inflammation, promote corneal healing, and prevent fibrosis positions it as a critical adjunctive therapy in both acute and chronic ocular surface disease management.

By addressing these clinical, logistical, and economic considerations, patch-AMT has the potential to become a mainstay therapy in ocular surface disease management, expanding its role beyond complex surgical cases to routine early intervention strategies that improve patient outcomes and preserve vision.

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Declarations

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Ethical Approval. This narrative review is based entirely on previously published literature and does not contain any studies with human participants or animals performed by the authors. Ethics compliance is therefore not applicable.

GLOSSARY

Stromal Haze	A loss of corneal transparency caused by extracellular matrix deposition and myofibroblast activation, often due to inflammation or trauma
Keratocyte Apoptosis	Programmed cell death of corneal stromal cells, typically triggered by inflammation, resulting in tissue degradation and delayed healing
Basement Membrane (BM)	A layer of extracellular matrix between the corneal epithelium and stroma that provides structural support and facilitates epithelial adhesion
Transforming growth factor beta (TGF-β)	A cytokine involved in wound healing and fibrosis, promoting extracellular matrix deposition and myofibroblast differentiation
Photorefractive keratectomy (PRK)	A laser refractive surgery that reshapes the cornea by removing the epithelium to correct vision errors
Persistent Epithelial Defect (PED)	A corneal wound that fails to heal in the normal timeframe, often linked to underlying conditions
Matrix metalloproteinases (MMP)	Enzymes that degrade extracellular matrix proteins, aiding in wound healing but also contributing to tissue damage when overactive
Limbal Stem Cell Deficiency (LSCD)	A deficiency of limbal stem cells that impairs corneal epithelial regeneration, leading to persistent epithelial defects
Neurogenic Inflammation	Inflammation triggered by nerve activation, involving the release of neuropeptides such as substance P, which exacerbate pain and immune responses
Quality-adjusted life year (QALY)	A metric combining the quality and quantity of life gained from a healthcare intervention, often used in cost-effectiveness analyses
Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)	Severe immune-mediated disorders that affect the skin and mucous membranes, including the ocular surface, causing inflammation and scarring

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