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ORIGINAL RESEARCH ARTICLE

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Condividere percorsi diagnostici e terapeutici nell'ipertensione arteriosa polmonare: una roadmap per il Triveneto

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Sharing Diagnostic and Therapeutic Pathways in Pulmonary Arterial Hypertension: A Roadmap for the Triveneto Region

Background: Pulmonary arterial hypertension (PAH) is a rare and progressive disease characterized by high mortality and a significant impact on quality of life. Despite therapeutic advances, considerable heterogeneity persists in Italy's diagnostic and therapeutic pathways, leading to delays in diagnosis and disparities in access to care.
Objective: With this work we aim to define a roadmap for a shared diagnostic, therapeutic, and care pathway for PAH in the Triveneto region, aiming to reduce management variability, improve continuity of care, and optimize the use of available resources.
Methods: A multidisciplinary group of cardiologists, pulmonologists, and rheumatologists from Triveneto, along with a representative from the Pulmonary Hypertension Patients' Association, convened in a series of meetings to discuss diagnostic and therapeutic pathways.
Results: Early identification of PAH should be based on the classification of symptomatic patients into three main phenotypes (cardiac, pulmonary, and not better specified), followed by a specific diagnostic process based on updated hemodynamic criteria.
Therapeutic strategies should be defined according to risk stratification, with clear guidelines for comorbidity management and monitoring through quality indicators (Key Performance Indicators) to assess the effectiveness of care pathways.
Conclusions: The proposed roadmap represents a shared model for PAH management in the Triveneto region, promoting a multidisciplinary and integrated approach. Its adoption could enhance care quality, reduce regional disparities, and align with European guidelines, ultimately improving patient prognosis and quality of life.

Keywords: Cardiology, Diagnostic and therapeutic pathway, Pneumology, Pulmonary arterial hypertension (PAH), Quality of life

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Introduzione

L'ipertensione arteriosa polmonare (IAP) è una patologia cronica rara e progressiva, caratterizzata dal rimodellamento vascolare ostruttivo delle piccole arterie polmonari muscolari, isolato o indotto da trigger. La prevalenza e l'incidenza

stimate nel mondo occidentale sono rispettivamente di circa 50 casi per milione di adulti e di 5-10 casi per milione per anno (1,2). La diagnosi richiede la conferma finale tramite procedura invasiva di cateterismo destro e, per il corretto inquadramento clinico-strumentale del paziente, è necessario un work-up a monte del dato emodinamico, che deve essere condotto con un approccio sistematico, multiparametrico e multidisciplinare. Le Linee Guida europee per la diagnosi e il trattamento dell'IAP, la cui l'ultima versione è stata pubblicata nel 2022, classificano la patologia sulla base dei processi fisiopatologici, della presentazione clinica, delle caratteristiche emodinamiche e dell'approccio terapeutico farmacologico e non farmacologico (1).

Si stima che in Italia i pazienti con IAP siano circa 3.500 (3). L'IAP è più frequentemente riscontrata nei giovani e nelle donne, ma recentemente vi è una crescente quota di pazienti più anziani, spesso maschi di età ≥ 65 anni. L'accentuata sensibilità alla problematica da parte della comunità medica sta determinando un cambiamento delle caratteristiche dei pazienti con IAP, che sono progressivamente più complessi e con un carico non trascurabile di comorbilità (2). L'IAP è una condizione potenzialmente fatale se non trattata tempestivamente con la terapia adeguata e impatta significativamente sulla qualità di vita (QdV) dei pazienti (4).

I progressi terapeutici degli ultimi anni hanno determinato un miglioramento nell'aspettativa di vita dei pazienti con IAP, con una sopravvivenza a 5 anni che è passata dal 34% nel 1991 a più del 60% nel 2015 (5). Tuttavia, in Italia sono ancora presenti notevoli difficoltà diagnostiche e gestionali, in quanto il trattamento dell'IAP è caratterizzato da una notevole eterogeneità, riflettendo variazioni significative nei percorsi clinici a livello regionale e tra i diversi presidi ospedalieri. Tale variabilità si traduce per i pazienti in un possibile ritardo diagnostico, in disparità di accesso alle cure e in difficoltà a essere correttamente seguiti nel follow-up. Alcune regioni italiane hanno sviluppato dei percorsi diagnostici terapeutici e assistenziali (PDTA) specifici per la gestione dell'IAP (6-8). In Triveneto sono presenti diversi centri per la presa in carico e la gestione dei pazienti con IAP, ma non è attualmente presente un percorso definito e condiviso, che descriva la sequenza degli accertamenti per l'intercettazione e la diagnosi della patologia e la gestione terapeutica in base alle specifiche caratteristiche del paziente, includendo anche indicatori di qualità (IQ). La definizione e il raggiungimento di tali indicatori consentirebbero di confrontare i risultati della pratica clinica con misure standardizzate, permettendo di identificare aree di intervento e di miglioramento (9). Un percorso condiviso per la gestione del paziente con IAP deve anche prevedere l'inclusione di modalità per la valutazione del tipo e della qualità dell'assistenza al paziente, attraverso la verifica della QdV e del livello di soddisfazione dello stesso.

Sulla base di queste necessità un gruppo di specialisti cardiologi, pneumologi e reumatologi del Triveneto, con il supporto dell'Associazione Malati Ipertensione Polmonare (AMIP), si è riunito in una serie di incontri per proporre una flow-chart che includa sia il percorso diagnostico che quello terapeutico del paziente con IAP. Gli obiettivi finali del percorso standardizzato sono quelli di ridurre la variabilità diagnostica e terapeutica e di fornire chiari riferimenti di strutture e di figure professionali per poter assicurare continuità e omogeneità delle cure ottimizzando le risorse a disposizione. Questa roadmap potrà essere un punto di riferimento per la gestione dei pazienti e per la condivisione di PDTA regionali.

Metodi

La stesura delle flow-chart per la diagnosi e il trattamento dell'IAP è stata il risultato di un confronto strutturato in 4 incontri del gruppo di lavoro del Triveneto. Il consenso è stato raggiunto attraverso discussioni iterative tra i partecipanti. I partecipanti al progetto sono esperti nella gestione dell'IAP, specialisti nelle discipline di cardiologia, pneumologia e reumatologia e attivi nei principali centri del Triveneto, con conoscenza delle strutture del territorio. Nel primo incontro, virtuale, sono stati identificati i principali temi del percorso diagnostico-terapeutico. Durante un secondo meeting, svolto in presenza, il gruppo si è diviso in due tavoli paralleli (diagnostico e terapeutico), con una distribuzione bilanciata delle competenze, per elaborare una prima bozza delle rispettive sezioni. Questa bozza è stata condivisa e discussa nel corso di un terzo meeting virtuale, a cui ha fatto seguito un quarto e ultimo meeting virtuale in cui i contenuti sono stati rivisti e finalizzati. Le eventuali discordanze sono state risolte attraverso l'individuazione di elementi comuni condivisibili da tutti oppure mediante la proposta di opzioni alternative.

Caratteristiche fondamentali per l'identificazione di un percorso standardizzato

Gli aspetti chiave considerati per la definizione del percorso per i pazienti con IAP sono:

- caratteristiche del percorso diagnostico;
- gestione terapeutica e follow-up clinico-strumentale;
- caratteristiche dei "centri dedicati all'IAP", sia per la presa in carico e il follow-up che per l'interazione con i centri del territorio;
- aspetti assistenziali.

Le Linee Guida europee sono state tenute in considerazione come riferimento per tutti i punti identificati, contestualizzandone i contenuti nella realtà dei centri del Triveneto (1).

Percorso diagnostico

I percorsi diagnostici coerenti con le Linee Guida (1) si basano sull'analisi dei sintomi e sul sospetto clinico. Per facilitarne l'applicazione, sono state individuate tre categorie di pazienti sintomatici, in base alle caratteristiche cliniche e al profilo di rischio: i) con fenotipo cardiaco; ii) con fenotipo pneumologico; iii) senza apparente rischio specifico. Per ciascuna categoria è stato disegnato un percorso diagnostico specifico, adattato alle diverse esigenze del paziente (Fig. 1). Il percorso diagnostico prende avvio da sintomi generici, come la dispnea, e ha l'obiettivo di orientare il processo fin dal primo contatto medico, che può avvenire presso il Medico di Medicina Generale (MMG) o, in ambito ospedaliero, con il Medico del Pronto Soccorso.

i) Fenotipo cardiaco: pazienti con un rischio elevato di patologie cardiovascolari, sia per precedenti eventi cardiovascolari sia per la presenza di fattori di rischio specifici, come ipertensione arteriosa essenziale o diabete mellito di tipo 2. Oltre alla valutazione clinica, è previsto un percorso diagnostico mirato che include l'esecuzione di un elettrocardiogramma e l'analisi dei livelli di peptidi natriuretici (BNP/NT-proBNP), test fondamentali per identificare e monitorare eventuali problematiche cardiache.
ii) Fenotipo pneumologico: pazienti con fattori di rischio polmonare come storia di fumo o esposizione a polveri.
iii) Pazienti sintomatici con fenotipo sospetto o non definito: sono inclusi anche i pazienti con una storia di pregressa embolia polmonare. Per quest'ultima categoria, la scelta dei test diagnostici sarà modulata in base alle caratteristiche individuali del paziente, mentre l'eventuale invio a un centro per l'IAP sarà determinato dai risultati degli accertamenti effettuati (Fig. 1).

Per i fenotipi cardiaco e polmonare l'iter diagnostico si conclude nel caso in cui venga identificata un'altra causa prettamente cardiologica o pneumologica che giustifichi la presentazione clinica. Diversamente, è fondamentale considerare l'ipotesi IAP alla base della sintomatologia. Pertanto, il percorso diagnostico successivo, riassunto nella Figura 1, dovrebbe essere avviato, includendo, se necessario, il riferimento del paziente a un centro per l'IAP per una gestione adeguata, soprattutto se l'ecocardiogramma suggerisce un'elevata probabilità di IAP.

Interazione centro IAP e territorio

È essenziale instaurare un canale di comunicazione aperto e collaborativo tra i centri per l'IAP e i centri territoriali, per poter valutare caso per caso eventuali deroghe al protocollo stabilito, in particolare riguardo alla distribuzione delle responsabilità diagnostiche. Per esempio, nei pazienti con una presentazione clinica grave e un forte sospetto di IAP, la decisione per un riferimento precoce al centro per l'IAP per la presa in carico e l'eventuale inizio di una terapia infusiva deve essere sempre concordata direttamente tra le parti coinvolte, garantendo così una gestione tempestiva e appropriata. L'esecuzione dei test diagnostici può essere effettuata presso i centri territoriali, a condizione che possano essere gestiti facilmente in tempi brevi. In alternativa, per esempio per test ad alta specificità come il test genetico, si rende opportuno un riferimento tempestivo al centro, in modo da garantire al più presto la presa in carico. In caso di paziente riferito dopo esecuzione dei test diagnostici, il centro IAP eseguirà una valutazione approfondita, con ripetizione dell'ecocardiogramma, sia per confermare la diagnosi che per raccogliere ulteriori dati utili per il monitoraggio a lungo termine.

Cateterismo cardiaco destro e test di vasoreattività

Il cateterismo destro rappresenta il gold standard per la diagnosi e la classificazione dell'ipertensione polmonare, inclusa l'IAP, e costituisce la fase finale di un iter diagnostico completo, ragionato e supportato da evidenze preliminari. Le più recenti Linee Guida hanno introdotto modifiche significative nei cut-off emodinamici utilizzati per la diagnosi e la classificazione dell'ipertensione polmonare, abbassando la soglia della pressione arteriosa polmonare media (mPAP) da 25 mmHg a 20 mmHg. Questa revisione ha l'obiettivo di migliorare la sensibilità diagnostica, consentendo un'identificazione più precoce delle condizioni patologiche (Tab. 1) (1). Il cateterismo destro è fondamentale per la diagnosi dell'IAP, richiede una competenza specifica da parte sia del centro che degli operatori coinvolti e deve essere eseguito seguendo protocolli rigorosamente standardizzati. Per garantire accuratezza e sicurezza, è raccomandato che il cateterismo destro venga effettuato esclusivamente in centri specializzati, dotati della competenza necessaria per la gestione completa dell'IAP, dalla diagnosi al trattamento.

TABELLA 1 - Definizioni emodinamiche dell'ipertensione polmonare

Definizione	Caratteristiche emodinamiche
Ipertensione polmonare	mPAP > 20 mmHg
Ipertensione polmonare pre-capillare	mPAP > 20 mmHg PAWP ≤ 15 mmHg PVR > 2 WU
Ipertensione polmonare post-capillare isolata	mPAP > 20 mmHg PAWP > 15 mmHg PVR ≤ 2 WU
Ipertensione polmonare combinata pre- e post-capillare	mPAP > 20 mmHg PAWP > 15 mmHg PVR > 2 WU
Ipertensione polmonare da esercizio	Pendenza mPAP/CO tra riposo ed esercizio > 3 mmHg/L/min

CO: gittata cardiaca; mPAP: pressione arteriosa polmonare media; PAWP: pulmonary arterial wedge; PVR: resistenza vascolare polmonare; WU: Wood units.

L'esecuzione del test di vasoreattività polmonare mediante ossido nitrico è in linea con le raccomandazioni delle Linee Guida (1). Nei pazienti con diagnosi di connettivopatia e sospetta IAP, il test di vasoreattività non risulta indicato (1).

Tipologie particolari di pazienti asintomatici per cui considerare esami di screening

- I pazienti con sclerosi sistemica presentano una maggiore prevalenza di IAP (10). Si raccomandano pertanto lo screening ecocardiografico sistematico e la spirometria con diffusione del monossido di carbonio (DLCO) a cadenza annuale, con eventuale personalizzazione a cadenza semestrale in casi particolari ad alto rischio.
- I familiari di primo grado dei pazienti con forma ereditaria (evidenza di mutazione genetica causale/verosimilmente causale) di IAP devono essere sottoposti a uno screening sistematico ecocardiografico annuale. Per i familiari dei pazienti con forme idiopatiche senza evidenza di varianti genetiche causali, lo screening sistematico non è

raccomandato. In caso di comparsa di sintomatologia è necessario avviare tempestivamente l'iter diagnostico per escludere una forma di IAP.
- I pazienti con epatopatia in attesa di trapianto di fegato vanno sottoposti a un ecocardiogramma di screening.
- Per i pazienti con HIV non vi sono solide evidenze per raccomandare l'esecuzione di screening periodici, i quali vanno pertanto concordati con le strutture che hanno in carico questi pazienti; in ogni caso gli accertamenti vanno eseguiti rapidamente in caso di sintomi sospetti.
- Per l'esclusione della forma di ipertensione polmonare tromboembolica cronica (CTEPH) nei pazienti con pregressa embolia polmonare (EP) recente, una rivalutazione ecocardiografica mirata a escludere forme di ipertensione polmonare di tipo 4 è raccomandata in caso di persistenza/ricomparsa di dispnea dopo i 3 mesi dopo la diagnosi di EP. Inoltre la rivalutazione ecocardiografica e il dosaggio del BNP/NT-proBNP possono essere utili nei pazienti dimessi dall'evento acuto con segni ecocardiografici di ipertensione polmonare e/o di disfunzione ventricolare destra.

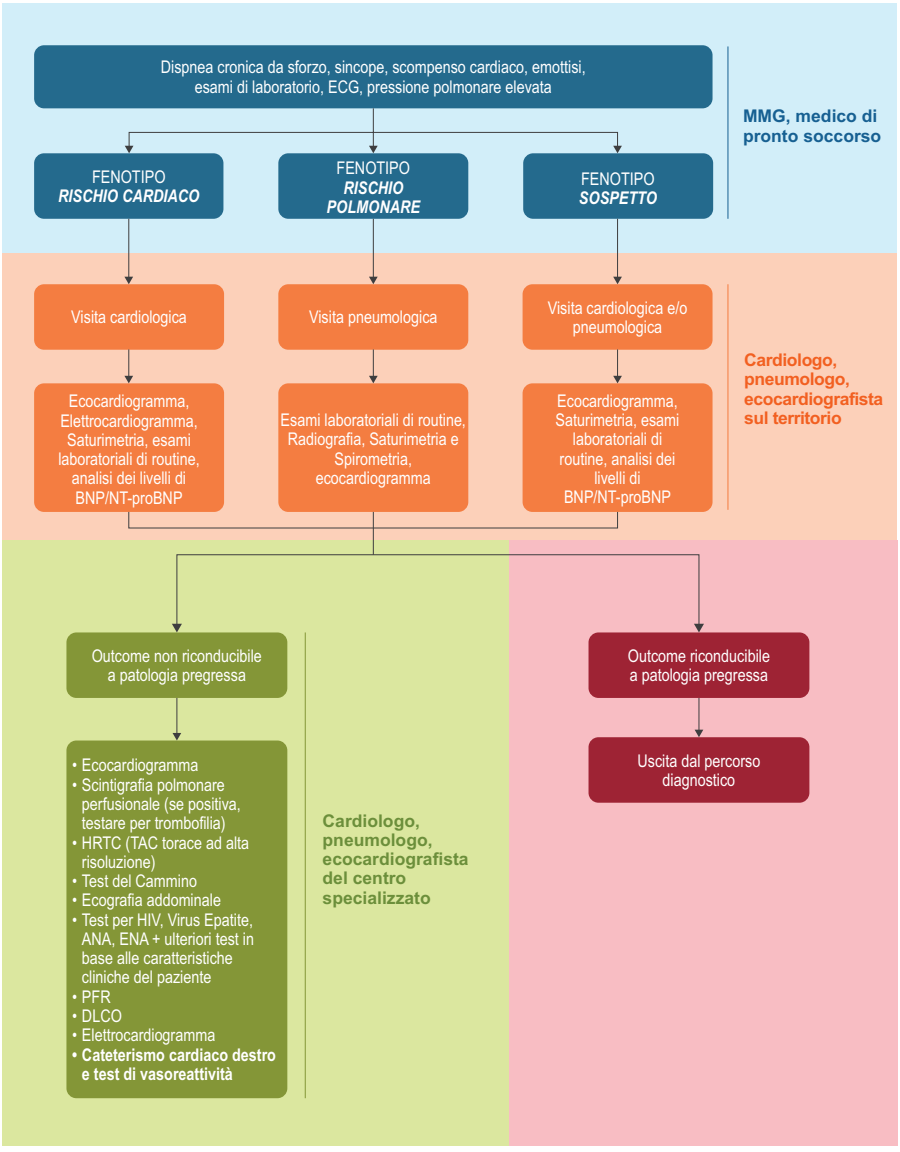

FIGURA 1 - Flow-chart suggerita per l'inserimento in un percorso diagnostico per il paziente con sospetto di ipertensione arteriosa polmonare.

Figure professionali, team multidisciplinare

La gestione dell'IAP richiede un approccio integrato e coordinato, in cui la collaborazione tra diverse figure professionali è essenziale per garantire un percorso diagnostico-terapeutico efficace. Negli accertamenti di primo livello sono coinvolti il MMG, lo pneumologo, il cardiologo, il medico di medicina interna, il radiologo e il medico di medicina d'urgenza e di Pronto Soccorso.

In caso di test primari positivi, per la conferma della diagnosi il paziente viene avviato a un centro per l'IAP, che

deve avvalersi di un team multidisciplinare per il completamento dell'iter diagnostico, l'inizio del percorso terapeutico e il supporto assistenziale al paziente e alla famiglia nel follow-up. Il team multidisciplinare deve includere: cardiologo, pneumologo, reumatologo, infermiere dedicato, radiologo e specialista del supporto psicologico/sociale (1). Ulteriori figure professionali possono essere coinvolte per casi specifici (p. es., cardiochirurgo, anestesista, infettivologo, epatologo, genetista). Il farmacista dovrebbe essere coinvolto data la frequente complessità che si riscontra nella prescrizione, nell'erogazione e nella gestione delle terapie vasoattive a livello ospedaliero e territoriale.

La frequenza dei meeting del team multidisciplinare deve essere adattata all'organizzazione del centro, al volume dei casi trattati e alle necessità specifiche dei pazienti. Nel caso in cui uno o più degli specialisti non avessero la possibilità di partecipare in presenza, è necessario considerare modalità di consulto a distanza, garantendo un confronto efficace. Gli specialisti dei centri territoriali che hanno inviato il paziente al centro per l'IAP dovrebbero essere attivamente coinvolti nei meeting e nelle discussioni cliniche, per favorire una gestione ottimale e condivisa del paziente. Inoltre, gli esiti delle discussioni del team multidisciplinare devono essere documentati in modo sistematico, insieme alla casistica affrontata, per assicurare tracciabilità, trasparenza e un controllo continuo sui volumi gestiti dal centro. Questo approccio permette di monitorare l'efficacia del team e di migliorare la qualità delle cure.

Indicatori di qualità

Per garantire un percorso diagnostico efficace e standardizzato, è fondamentale definire specifici indicatori di qualità che permettano di monitorare e di migliorare continuamente la gestione dei pazienti. Per il percorso diagnostico si identificano i seguenti indici di qualità:

- ~90% dei pazienti presi in carico entro 30 giorni rispetto ai pazienti riferiti;
- ~90% dei pazienti che, una volta confermata l'appropriatezza della presa in carico, completano l'iter diagnostico entro 45 giorni (in caso di festività intermedie oppure di particolari periodi di pletora);
- ~90% dei pazienti che iniziano la terapia specifica per IAP e che hanno eseguito un iter diagnostico completo e conclusivo entro 60 giorni

Nella Figura 2 sono riportati alcuni punti da tenere in considerazione nella diagnosi e gestione dell'Ipertensione Arteriosa Polmonare

Percorso terapeutico e follow-up

Scelta terapeutica

La definizione della terapia appropriata e il suo inizio precoce avvengono in seguito alla stratificazione del rischio secondo le Linee Guida (1).

Per l'avvio della terapia, oltre alla classe di rischio è fondamentale considerare il risultato del test di vasoreattività e le eventuali comorbilità, identificando:

- i pazienti con comorbilità cardiovascolare: obesità, diabete, ipertensione arteriosa, coronaropatia, vasculopatia periferica, fibrillazione atriale;
- i pazienti con comorbilità polmonare: valutati in collaborazione con lo pneumologo, il quale, sulla base dei risultati dell'HRCT e della spirometria con DLCO, determina l'entità della patologia respiratoria. Nei casi in cui la pneumopatia risulti lieve, i pazienti dovrebbero essere gestiti come se fossero privi di comorbilità significative.

L'indicazione alla terapia specifica per IAP nel paziente con comorbilità va definita caso per caso, considerando la possibilità di avviare in un primo momento una monoterapia e valutando la successiva implementazione.

Oltre all'avvio della terapia, è fondamentale per ogni paziente condividere la gestione della stessa, con attenzione alla presenza di assistenza domiciliare, al monitoraggio e al follow-up. Per monitorare la QdV dei pazienti, si suggerisce di utilizzare il questionario emPHasis10 (11) sia al baseline che ad ogni successiva rivalutazione clinica del paziente.

La Figura 3 riporta la flow-chart del percorso terapeutico. I pazienti con test di vasoreattività positivo vengono indirizzati a una terapia con Ca^{++} antagonisti che devono essere titolati a elevati dosaggi come previsto dalle Linee Guida (1). Per i pazienti con test di vasoreattività negativo, il percorso prevede una valutazione della presenza e dell'entità delle comorbilità, seguita dalla valutazione del rischio, al fine di definire l'approccio terapeutico più appropriato. I pazienti con connettivopatia, per i quali il test non è indicato, seguono il percorso di quest'ultimo gruppo, tenendo presente che vi possono essere in questo caso delle comorbilità legate alla malattia stessa (miocardiopatia e/o interstiziopatia polmonare sclerodermica), come per esempio l'interessamento del microcircolo coronarico con rischio di disfunzione diastolica subclinica del ventricolo sinistro;

- i pazienti a rischio alto, dovrebbero essere ricoverati per l'inizio precoce di una triplice terapia di combinazione comprensiva di prostanoide parenterale. È suggeribile anche l'avvio dell'iter per l'inserimento in lista d'attesa di trapianto di polmone, presentando il caso al centro più vicino (per l'area triveneta il centro trapianti di Padova), per poter garantire possibilità future di trapianto al paziente in terapia con prostanoidi parenterali. I candidati al trapianto devono essere in grado di trarre il massimo beneficio dall'organo trapiantato. Purtroppo i criteri per la gestione della lista d'attesa per trapianto bipolmonare non favoriscono i malati di IAP, che normalmente arrivano al trapianto solo in una fase terminale della malattia;
- i pazienti a rischio intermedio e basso che non presentino significative comorbilità, vanno avviati a una terapia di combinazione orale con ERA e PDE5i.

Al momento dell'inizio della terapia specifica per l'IAP, il MMG deve essere tempestivamente informato. Questo può avvenire tramite l'invio di un documento redatto dallo specialista e trasmesso via e-mail. Il MMG rappresenta un punto di riferimento fondamentale per il paziente e il suo coinvolgimento pro-attivo è essenziale per garantire una piena

Punti di attenzione

•L'esecuzione e interpretazione dell'ecocardiogramma di pazienti con sospetta IAP richiede competenze specifiche: è fortemente consigliato ripetere l'esame **ecocardiografico** nel **centro per l'IAP** per i pazienti riferiti, anche in presenza di un esame già eseguito

•In seguito a risultati postivi dei primi accertamenti e visita specialistica, si consiglia il contatto con **gli specialisti dei centri di IAP**

•**Test Genetico**: una volta confermata la diagnosi di IAP ed escluse le forme associate, il centro di riferimento per l'IAP dovrebbe considerare l'esecuzione sistematica del test genetico per tutti i pazienti. Questo approccio è particolarmente rilevante in presenza di possibili implicazioni per la diagnosi precoce nei familiari, come ad esempio nei figli (1, 11). L'esecuzione del test genetico richiede la disponibilità del servizio specifico e la presenza di un **team dedicato**, comprensivo di genetisti. La gestione dei risultati e il **counselling** devono essere svolti in modo integrato e condiviso tra **lo specialista** responsabile della gestione clinica e il **genetista**. Lo **screening familiare** a cascata deve essere implementato per i familiari di primo grado dei pazienti con test positivo e conferma di essere portatori della mutazione. Questo screening, effettuato tramite **ecocardiogrammi periodici**, deve essere gestito dal centro di riferimento per l'IAP che segue il paziente. Inoltre, il centro per l'IAP deve garantire una **rivalutazione genetica periodica** durante il follow-up del paziente. Questo aspetto è cruciale, poiché il contributo delle mutazioni genetiche alla progressione della malattia può variare nel tempo, rendendo necessario un monitoraggio continuo.

•È fondamentale supportare il paziente informandolo sull'importanza di sottoporsi alle **vaccinazioni** contro influenza, pneumococco e Covid, sottolineando i benefici in termini di **prevenzione delle complicanze**.

•Per le pazienti in età fertile, è essenziale fornire informazioni dettagliate sui rischi significativi associati a eventuali **gravidanze** e discutere le opzioni disponibili per una contraccezione sicura ed efficace. In caso di gravidanza la paziente dovrebbe essere **seguita e monitorata presso centro di riferimento per IAP** dati gli elevati rischi connessi alla gravidanza e al parto.

FIGURA 2 - Punti di attenzione nella gestione dell'ipertensione arteriosa polmonare.

consapevolezza della malattia e una gestione condivisa del percorso terapeutico.

Terapia infusiva

L'inizio della terapia infusiva in un paziente senza comorbilità, ma a rischio alto, deve essere tempestivo, evitando qualsiasi forma di inerzia terapeutica (12). Questo passaggio rappresenta un momento delicato nella vita del paziente ed è consigliabile valutare l'intervento da parte dello specialista psicologo per supportare il paziente nella comprensione e nell'accettazione della malattia e delle terapie proposte. Il paziente dovrebbe ricevere un adeguato supporto psicologico, fornito da un'equipe specializzata, se presente nella struttura. Si suggerisce il contatto con le Associazioni di Malati (AIPI e AMIP), che possono fornire il sostegno adeguato attraverso una help-line telefonica e il supporto dell'esperienza di pazienti già in cura. Il medico che interagisce con il malato di ipertensione polmonare dovrebbe utilizzare una modalità di comunicazione empatica; deve essere realista ma al tempo stesso tenere una porta aperta alla speranza.

Indicatori di qualità

Affinché si possa definire una gestione efficace dell'inizio di terapia del paziente, devono essere raggiunti i seguenti indicatori di qualità:

- il 100% dei pazienti con test di vasoreattività positivo deve essere avviato a una terapia con Ca^{++} antagonista;
- il 100% dei pazienti senza comorbilità a rischio basso o intermedio deve iniziare una terapia di combinazione orale ERA + PDE5i entro un mese dalla diagnosi;
- a una percentuale di pazienti superiore al 90% fra coloro che non presentano comorbilità con un rischio alto va offerta la terapia infusiva con un prostanoide;

- a una percentuale di pazienti superiore al 90% fra i malati di età < 65 anni cui viene iniziata una terapia infusiva con prostanoide e privi di controindicazioni assolute va proposto l'inserimento in lista d'attesa per trapianto polmonare.

Follow-up

Il primo follow-up deve essere eseguito a 3 mesi dall'inizio della terapia e successivamente ogni 3-6 mesi, con la definizione della classe funzionale WHO, l'esecuzione dell'elettrocardiogramma, del test del cammino (6MWT) e/o del test da sforzo cardiopolmonare (CPET), il dosaggio del NT-proBNP e l'ecocardiogramma, per ri-stratificare la classe di rischio del paziente in terapia medica specifica; l'eventuale nuova esecuzione del cateterismo destro deve essere valutata caso per caso, prima di potenziare la terapia nel paziente che non raggiunga una classe di rischio basso.

Il test CPET è raccomandato nei pazienti giovani invece del test del cammino, in quanto il 6MWT tende a sottostimare l'importanza della limitazione all'esercizio dei soggetti più giovani.

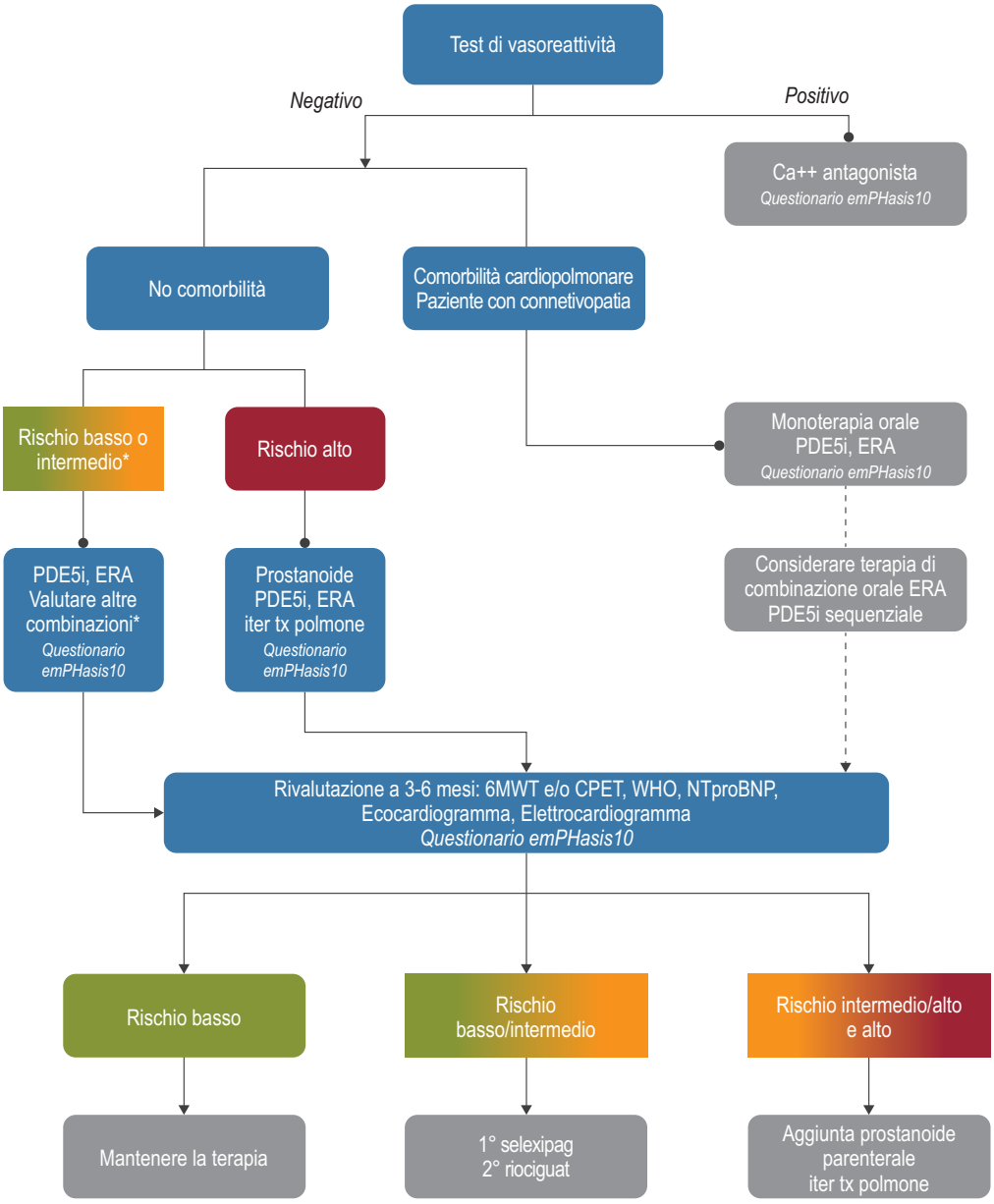

FIGURA 3 - Flow-chart per la definizione della terapia nei pazienti con IAP.

*evitare se possibile l'utilizzo della combinazione bosentan sildenafil

Per il paziente che all'ecocardiogramma presenti una dilatazione dell'arteria polmonare oltre i 4,5 cm e/o sintomi sospetti per angina, è suggeribile l'esecuzione di un'angio-TAC per lo studio delle coronarie, per escludere fenomeni di compressione sul tronco comune della coronaria di sinistra.

Al paziente che nel follow-up permanga a rischio intermedio-basso (secondo la Tabella del rischio a 4 strati) in terapia di combinazione orale vanno offerti la terapia con selexipag oppure lo switch da PDE5i a riociguat.

Il paziente che nel follow-up presenti un rischio intermedio-alto o alto va avviato a una terapia con prostanoide. La valutazione del rischio va integrata con dati ecografici, emodinamici o CPET (a seconda dei casi). È noto che la valutazione del rischio con la Tabella a 4 strati e 3 parametri sottovaluti il rischio nel paziente più giovane e sovrastimi il rischio attribuibile all'IAP nell'anziano con comorbilità.

In previsione della prossima disponibilità di sotatercept, farmaco che costituisce una quarta via terapeutica completamente nuova in quanto non agisce come vasodilatatore ma riequilibrando il rapporto tra proliferazione e apoptosi cellulare (13), lo specialista dell'ipertensione polmonare dovrà posizionare il farmaco come consentito dalla scheda tecnica. Gli atti del simposio mondiale 2024 (14,15) suggeriscono di introdurre sotatercept nel follow-up, nei pazienti a rischio intermedio-basso, intermedio-alto e alto. Per ciascun trattamento si consiglia di considerare i le possibili reazioni avverse ed ogni altra importante indicazione (Tab. 2) (15), consultando anche risorse online (16).

Percorso riabilitativo

Durante il follow-up, si raccomanda di includere in un percorso riabilitativo polmonare tutti i pazienti che non raggiungono una classe funzionale NYHA I. Tale percorso dovrebbe essere personalizzato, iniziando da una valutazione approfondita delle capacità funzionali del paziente. La riabilitazione deve essere adattata alle caratteristiche individuali, considerando fattori come età, genere, comorbilità presenti e gravità della malattia. Questo approccio mirato garantisce interventi riabilitativi più efficaci, migliorando il recupero funzionale e la qualità di vita del paziente.

Indicatori di qualità

Affinché si possa definire una gestione efficace del follow-up del paziente, devono essere raggiunti i seguenti indicatori di qualità:

- una percentuale di pazienti superiore al 90% valutata con 6MWT (o CPET), NT-proBNP e classe funzionale alle visite di follow-up;
- una percentuale di pazienti superiore al 90% a cui viene offerto un upgrade terapeutico (aggiunta di selexipag o switch da PDE5i a riociguat) in caso di rischio intermedio-basso al follow-up;
- una percentuale di pazienti superiore al 90% a cui viene offerto un upgrade terapeutico con prostanoide infusivo in caso di rischio intermedio-alto o alto al follow-up (in assenza di comorbilità significative).

Punti di attenzione

Terapia di supporto: l'indicazione a una terapia diuretica e anticoagulante, all'ossigeno-terapia e a una terapia analgesica per gli effetti collaterali del prostanoide va valutata caso per caso.

Gli effetti avversi e le interazioni farmacologiche principali relative ai farmaci per l'IAP dovrebbero essere condivisi con i MMG, in modo che possano essere consapevoli nell'ambito della gestione condivisa del paziente.

Le prescrizioni di esami per il follow-up clinico-ematico e strumentale dovrebbero essere fornite dal medico specialista.

Caratteristiche del centro per l'IAP

Il centro specializzato nella gestione del paziente con IAP deve garantire la possibilità di diagnosi, avvio della terapia e gestione del follow-up, e la presenza del team multidisciplinare indipendentemente dal volume di pazienti seguiti. Se il centro IAP non raggiunge una numerosità adeguata agli standard indicati dalle Linee Guida europee in ciascuno dei passaggi critici per la gestione del paziente, deve assicurare il collegamento con un centro di dimensioni più grandi che possa fornire il supporto necessario. Questo può e deve accadere soprattutto in caso di dubbi in fase di diagnosi ma anche nella gestione della terapia, particolarmente nei pazienti in classe di rischio elevato o intermedio-elevato. Per l'esecuzione del test genetico, l'avvio di una terapia infusiva, il trapianto bipolmonare e la riabilitazione, è fondamentale che ogni centro sia in collegamento con la struttura di riferimento che possiede l'esperienza necessaria per la corretta gestione.

La partecipazione a registri multicentrici e a studi clinici per l'IAP sono ulteriori requisiti che contribuiscono a conferire competenza gestionale a un centro. Il coinvolgimento in progettualità che riguardano la sfera della ricerca clinica, ma anche per soli scopi osservazionali, deve essere sistematicamente stimolato e promosso in modo da garantire il coinvolgimento diretto di tutti i centri indipendentemente dal numero dei pazienti in gestione.

Aspetti assistenziali

In caso di sospetto di IAP, il medico specialista che opera in un centro di riferimento riconosciuto può prescrivere, in regime di esenzione, tutte le indagini finalizzate alla diagnosi, riportando nella ricetta il codice R99 o R99999, a seconda della regione. Questo codice, che ha validità un mese, va utilizzato anche per le indagini genetiche rivolte ai parenti di primo grado dei pazienti con mutazione genetica nota.

Dopo la diagnosi, i centri di riferimento riconosciuti a livello regionale possono certificare la presenza di una patologia rara. Il codice di esenzione RG0120 può essere applicato alla patologia rara Ipertensione Arteriosa Polmonare (IAP idiopatica, ereditaria, da farmaci). L'esenzione relativa alla patologia rara Sclerosi Sistemica ha il codice RM0120. Il paziente affetto da IAP associata a sclerosi sistemica può ottenere l'esenzione dal reumatologo o dall'immunologo nel contesto del team multidisciplinare.

I codici di esenzione A02.416 ("malattie cardiache e del circolo polmonare") e A02.417 ("altre malattie del circolo

TABELLA 2 - Trattamenti farmacologici per l'iap (modificato da (15)) [d: i rif. Biblio dal 17 al 37 compresi si trovano all'interno di questa tabella]

Farmaci	Reazioni avverse comuni	Altre informazioni
Farmaci orali		
PDE5i (sildenafil, tadalafil) (17-20)	Mal di testa, vampate, dispepsia, epistassi	Raro rischio di perdita della vista o dell'udito. Evitare con nitrati, riociguat
Stimolatori della guanilato ciclasi (riociguat) (21)	Mal di testa, dispepsia, vertigini, ipotensione	Evitare in gravidanza[c], evitare con nitrati e PDE5i. Monitorare l'ipotensione; può essere necessario un aggiustamento della dose in base alla pressione arteriosa sistemica
Antagonisti del recettore dell'endotelina-1 (ambrisentan, bosentan, macitentan) (20,22-26)	Edema periferico, congestione nasale, anemia[a]	Evitare in gravidanza[c]. Monitorare l'emoglobina (tutti), la funzione epatica (mensilmente per bosentan, secondo indicazione clinica per gli altri)
Agonisti del recettore della prostaciclina (selexipag) (27)	Reazioni avverse di tipo prostanoide[b]	I dati su selexipag in gravidanza non sono disponibili
Prostanoidi orali (treprostinil, beraprost) (28-32)	Reazioni avverse di tipo prostanoide[b]	
Farmaci per via inalatoria		
Prostanoidi inalatori (iloprost, treprostinil) (33,34)	Tosse, reazioni avverse di tipo prostanoide[b]	
Farmaci parenterali		
Prostanoidi per via parenterale (epoprostenol [i.v.], treprostinil [i.v., s.c.]) (35,36)	Reazioni avverse di tipo prostanoide[b]	L'interruzione improvvisa dei prostanoidi per via parenterale può essere pericolosa per la vita
Inibitore del segnale dell'activina (sotatercept [s.c.]) (13,37)	Mal di testa, diarrea, epistassi, eventi emorragici, teleangiectasia	Evitare in gravidanza[c]; potenziale rischio di riduzione della fertilità futura basato su studi animali. Monitorare trombocitopenia e aumento dell'emoglobina per le prime cinque dosi e periodicamente

[a]Sebbene le reazioni avverse agli antagonisti del recettore dell'endotelina-1 tendano a essere effetti di classe, esiste una certa variabilità e il passaggio all'interno della stessa classe può essere considerato.
[b]Gli eventi avversi di tipo prostanoide includono vampate, mal di testa, dolore mandibolare, nausea/vomito e diarrea.
[c]Contraccezione altamente affidabile e test di gravidanza mensile richiesti per tutte le persone in età fertile a causa del rischio di teratogenicità.

polmonare") si applicano a tutti gli altri pazienti affetti da ipertensione polmonare (associata a cardiopatie congenite, HIV, schistosomiasi, IAP in un paziente con significative comorbilità e CTEPH). In caso di compromissione multiorgano, può essere utilizzato anche il codice di esenzione 049, che definisce un paziente con più patologie e danno multiorgano che determina una compromissione generale e della QdV.

Discussione

La gestione dell'IAP non è omogenea sul territorio italiano, con differenze anche a livello della stessa area. La mancanza di un percorso standardizzato può comportare ritardi diagnostici e terapie non ottimali. Le Linee Guida europee (1) suggeriscono un percorso generale per il paziente con IAP, che deve essere contestualizzato in ogni realtà locale. La condivisione di approcci diagnostici e terapeutici comuni mira a sviluppare un percorso standardizzato per la gestione dell'IAP nel Triveneto, per migliorare la prognosi dei pazienti. I centri per l'IAP presenti nella regione, grazie a una solida rete basata su conoscenze condivise, collaborazione multidisciplinare e scambio continuo di esperienze cliniche, rappresentano già una base efficace per l'implementazione di questo modello.

La crescente disponibilità e l'efficacia delle opzioni terapeutiche rendono fondamentale un accesso equo alle cure, con particolare attenzione ai pazienti complessi, come i pazienti anziani e i soggetti con comorbilità. La gestione dell'IAP richiede quindi competenze diverse (cardiologo, pneumologo, reumatologo) e integrate all'interno del centro di riferimento specializzato, che possano garantire l'accesso a test diagnostici avanzati e a protocolli terapeutici mirati, oltre che al trapianto polmonare nei casi più gravi.

Gli approcci terapeutici devono avere come obiettivo il raggiungimento della classe di rischio più bassa per il paziente con IAP e il mantenimento di una buona QdV. Pertanto, è necessario migliorare anche il follow-up del paziente, mettendo a disposizione un supporto psicologico e assistenziale e un percorso riabilitativo.

Di fondamentale importanza per il follow-up risulta il contatto con l'Associazione di Pazienti, che si mette a disposizione

per un supporto pratico al paziente. Confronto con pazienti esperti, occasioni di incontro medico-paziente e linee dedicate per il supporto nella vita quotidiana sono iniziative organizzate dall'Associazione di Pazienti, di grande valore per tutte le persone con IAP. Il ruolo centrale dell'Associazione di Pazienti e dell'empowerment del paziente è sottolineato anche dalle Linee Guida (1) e nella realtà italiana la sua presenza è fondamentale per far fronte alle necessità anche psicologiche del paziente.

La possibilità di proporre un percorso riabilitativo ai pazienti con IAP è importante per la QdV del paziente con IAP. Esistono studi che sottolineano come la riabilitazione e l'esercizio fisico proposto in modo personalizzato possano migliorare la QdV correlata alla salute senza un aumento del rischio di eventi avversi gravi (38). Il counseling sulle attività che possono essere affrontate dal paziente con IAP dovrebbe essere fornito dai centri per l'IAP, con particolare attenzione anche alla comunicazione degli eventi avversi dei farmaci specifici e dell'elevato rischio di mortalità materna e fetale nel corso di un'eventuale gravidanza. L'IAP, secondo le Linee Guida, rappresenta una controindicazione alla gravidanza a priori oltre che in rapporto con la potenziale teratogenicità dei farmaci specifici (1,39).

L'assistenza al paziente con IAP comprende il supporto durante la terapia infusiva con prostanoide: devono essere garantite la semplicità nel ritiro dei farmaci, delle pompe e del kit per infusione presso un unico punto di ritiro (normalmente la farmacia) e, se possibile, l'attivazione di un'assistenza domiciliare. Questa viene usualmente garantita dalle aziende che distribuiscono treprostinil per infusione sottocutanea, attraverso aziende private di servizi alla persona. Per i pazienti in terapia con epoprostenolo è opportuno invece attivare, coinvolgendo il MMG, un'Assistenza Domiciliare Integrata (ADI).

Il centro di riferimento per l'IAP deve impegnarsi nella formazione del personale infermieristico per garantire una buona gestione del sistema di infusione e garantire un backup costante di reperibilità in caso di blocco improvviso e inatteso della pompa.

Questo lavoro presenta delle limitazioni. I metodi specifici di raccolta dei dati non sono stati dettagliati, ma l'implementazione di indicatori di qualità e il successivo confronto con standard nazionali e internazionali sono previsti nell'ambito della valutazione in corso dell'efficacia del percorso.

La definizione di flow-chart condivise per il percorso diagnostico e terapeutico è il primo passo per la definizione di un PDTA per il Triveneto, nell'ottica di una sempre crescente attenzione al paziente e alla gestione omogenea dell'IAP.

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ORIGINAL RESEARCH ARTICLE

Evoluzione dei trattamenti per l'angioedema ereditario in Italia: utilizzo del lanadelumab nella pratica clinica

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Evolution of Treatments for Hereditary Angioedema in Italy: Use of Lanadelumab in Clinical Practice

Introduction: Hereditary angioedema (HEA) is a rare genetic disorder characterised by recurrent episodes of edema affecting various body districts. HEA therapy includes treatment of acute attacks and short- or long-term prophylaxis.

Objective: To describe the main demographic and clinical characteristics of patients with HEA in real Italian clinical practice, as well as the use of pharmacological treatments, the use of healthcare resources and costs with particular reference to lanadelumab.

Methods: From administrative databases of healthcare institutions for about 9 million patients, between January 2010 and September 2020, all-age HEA patients were identified through hospitalisation, exemption code or specific drugs. Demographic and clinical characteristics, medications prescribed for acute attacks and prophylaxis were described at inclusion. For patients treated with lanadelumab, the switching of dosing regimen from 2 to 4 weeks was examined. Healthcare resource utilisation and costs were assessed at one-year follow-up.

Results: 258 patients with HEA were identified (~0.003% of the sample). Of them, 41.1% were male, and the mean age was 44.6 years; 80% of patients were treated for acute attacks, and 20% were on prophylaxis. In lanadelumab-treated, 85% started treatment with a 2-week regimen, and of them 75.8% switched to a 4-week regimen. For these patients, the estimated annual cost—calculated using the weighted average of patients who switched treatments—was €114,362.

Conclusions: The data from this analysis on therapeutic management of HEA patients in the Italian clinical practice showed that, despite the limited number of patients treated with lanadelumab, many received one administration every 4 weeks, suggesting a good disease control.

Keywords: Acute attacks, Healthcare costs, Hereditary angioedema, Lanadelumab, Prophylaxis

Introduzione

L'angioedema ereditario (AEE) è una malattia genetica rara dovuta al deficit (AEE di tipo I) o al malfunzionamento (AEE di tipo II) del C1-esterasi-inibitore (C1-INH) (1). Questo porta a una maggiore produzione di bradichinina in condizioni basali, che aumenta ulteriormente durante un attacco di angioedema, manifestandosi con episodi ricorrenti di gonfiore cutaneo, dolore addominale e talvolta ostruzione delle vie aeree superiori, rappresentando un pericolo per la vita a causa del coinvolgimento delle aree sottocutanee e delle sottomucose (2,3).

Si stima che l'incidenza dell'AEE a livello globale sia compresa tra una persona su 10.000 e una su 50.000, ma è probabile che vi siano numerosi casi non diagnosticati (4). Secondo i dati Orphanet, raccolti nel 2013, la prevalenza minima stimata di AEE era di 1 caso ogni 64.935 abitanti, basata su 920 pazienti identificati su una popolazione totale di 59.394.000 persone (4). Spesso, la malattia non viene riconosciuta per lungo tempo poiché i suoi sintomi possono essere confusi con quelli di condizioni più comuni come allergie o disturbi gastrointestinali. Le manifestazioni dell'AEE, che possono verificarsi frequentemente, solitamente durano dai 2 ai 5 giorni prima di scomparire (2).

La gestione della patologia comprende due approcci: il trattamento acuto degli attacchi e la prevenzione con terapie profilattiche a breve o a lungo termine (5). I trattamenti per gli attacchi acuti includono concentrati di C1-INH, derivati dal plasma o ricombinanti e antagonisti del recettore B2 della bradichinina (icatibant) (6). Gli androgeni attenuati e gli antifibrinolitici sono stati utilizzati per molti anni come trattamento di prima linea in profilassi, ma il loro impiego è sempre più limitato, soprattutto a causa della disponibilità di terapie più recenti con minori effetti avversi e una migliore efficacia (7).

Tra le terapie di profilassi a lungo termine, è stato introdotto un farmaco sottocutaneo, il lanadelumab, che blocca

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l'attività della callicreina plasmatica, riducendo così la quantità di bradichinina nel sangue e prevenendo i sintomi dell'AEE (8).

A oggi, sono pochi i dati sull'attuale utilizzo delle terapie per l'AEE nella pratica clinica italiana e gli studi disponibili sono stati pubblicati prima dell'approvazione del lanadelumab (9).

L'obiettivo dello studio è stato quello di condurre un'analisi epidemiologica della popolazione con AEE di tutte le età in Italia, finalizzata a descrivere le principali caratteristiche demografiche e cliniche dei pazienti, l'utilizzo dei trattamenti farmacologici, le pratiche terapeutiche più recenti, i percorsi di cura, le modalità di impiego dei farmaci, nonché l'utilizzo delle risorse sanitarie e i costi sostenuti dal Servizio Sanitario Nazionale (SSN) in un contesto di reale pratica clinica.

Metodi

Fonte dei dati

È stata condotta un'analisi osservazionale retrospettiva utilizzando i dati estratti dai flussi amministrativi di un campione di ASL distribuite sul territorio nazionale (4 nel Nord Italia, 8 nel Centro-Sud) con un bacino di assistiti di oltre 9 milioni di persone, corrispondente a circa il 15% della popolazione italiana, con dati disponibili dal 1° gennaio 2009 al 30 settembre 2023. L'analisi si è basata sui seguenti database amministrativi: Archivio Anagrafe Assistiti, per le caratteristiche demografiche (sesso, età) e l'eventuale data di decesso; Anagrafe Esenzioni, che contiene i codici di esenzione per ciascuna specifica patologia; Assistenza Farmaceutico-Territoriale (AFT) e Farmaci a Erogazione Diretta (FED), da cui sono stati ottenuti i dati (tra cui i codici di autorizzazione all'immissione in commercio, AIC, e l'Anatomical Therapeutic Chemical, ATC) dei trattamenti farmacologici erogati in regime di rimborsabilità da parte del SSN; Schede di Dimissione Ospedaliere (SDO) contenenti le informazioni standardizzate che descrivono i ricoveri effettuati dai pazienti oggetto dello studio, tra cui le diagnosi codificate mediante il sistema ICD-9-CM (International Classification of Diseases, 9th Revision Clinical Modification); Specialistica Pubblica Ambulatoriale, in cui sono riportati i dati riguardanti le visite specialistiche, i test laboratoristici e gli esami strumentali a cui il soggetto in studio è stato sottoposto e che sono stati erogati in regime di convenzione con il SSN.

La base dati utilizzata è costituita esclusivamente da dati anonimizzati. È stata ottenuta l'approvazione dei Comitati Etici di tutti gli Enti coinvolti, come riportato di seguito: autorizzazione BAT (Barletta Andria Trani) Comitato Etico interprovinciale Area I (protocollo n. 68/20, data di approvazione 3/12/2020); autorizzazione Berica Comitato Etico per le Sperimentazioni Cliniche (CESC) della Provincia di Vicenza (protocollo n. 1627, data di approvazione 28/10/2020); autorizzazione del Comitato Etico interprovinciale Area I di Bergamo (codice protocollo PROGETTO STREAM, data di approvazione 16/12/2022); autorizzazione Brindisi Comitato Indipendente di Etica Medica (protocollo n. 48148, data di approvazione 28/05/2021); autorizzazione Foggia Comitato Etico interprovinciale Area I (protocollo n. 63/20, data di approvazione 3/12/2020); autorizzazione Napoli 3 Comitato Etico Inter-aziendale Campania Sud (protocollo n. 51, data di approvazione 02/09/2020); autorizzazione Palermo Comitato Etico Palermo 1 (protocollo n. 02/2021, data di approvazione 24/02/2021); autorizzazione Pedemontana Comitato Etico per le Sperimentazioni Cliniche (CESC) della Provincia di Vicenza (protocollo n. 0036999, data di approvazione 28/04/2021); autorizzazione CE Roma 5 Comitato Etico "Lazio 1" (protocollo n. 1166/CE Lazio 1, data di approvazione 12/10/2020); autorizzazione Roma 6 Comitato Etico "Lazio 2" (protocollo n. 0216084/2020, data di approvazione 16/12/2020); autorizzazione Serenissima Comitato Etico per la Sperimentazione Clinica della provincia di Venezia e IRCCS S. Camillo (28/07/2020); autorizzazione del Comitato Etico Inter-aziendale Campania Sud di Salerno (protocollo n. 64, data di approvazione 03/11/2020).

Popolazione in studio

Sono stati selezionati tutti i pazienti con diagnosi di AEE tra gennaio 2010 e settembre 2022. L'intervallo temporale è stato definito per garantire l'omogeneità dei dati disponibili nei database delle ASL partecipanti. La scelta di non includere pazienti successivi a settembre 2022 è stata motivata dall'esigenza di assicurare almeno un anno completo di follow-up per ciascun soggetto incluso nello studio. Per l'identificazione dell'AEE, sono stati utilizzati uno o più dei seguenti criteri (proxy di diagnosi), come precedentemente descritto da Giacomini et al. (9): (i) almeno un codice di esenzione attivo per AEE (codice RC0190); e/o (ii) almeno una prescrizione di farmaci indicati per il trattamento dell'AEE (ATC B06AC01: C1-INH da plasma umano o ricombinante; e/o ATC B06AC02: icatibant; e/o ATC B06AC05: lanadelumab); e/o (iii) almeno una prescrizione di danazolo (ATC G03XA01) o acido tranexamico formulazione orale (ATC B02AA02; AIC 021458017, 022019018, 022019020, 044063067), insieme ad almeno un ricovero con diagnosi di dimissione con codici ICD-9-CM 277.6 e 279.8. La data della prima prescrizione di uno dei farmaci elencati o del primo codice di esenzione attivo per AEE nel periodo di inclusione è stata considerata come data-indice. Come periodo di caratterizzazione è stato considerato un intervallo di almeno 12 mesi prima della data-indice. Dal momento che il periodo di inclusione non coincide con l'inizio della disponibilità dei dati (1° gennaio 2009), la durata della caratterizzazione retrospettiva può variare tra i 12 mesi minimi richiesti e durate superiori, a seconda della data di inclusione (data-indice) del singolo paziente. Il follow-up comprendeva tutto il periodo disponibile dopo la data-indice, garantendo almeno un anno di dati per ciascun paziente. Per l'analisi del percorso terapeutico dei pazienti è stato considerato l'intero follow-up disponibile, al fine di valutare in modo accurato le variazioni nei regimi di dosaggio nei soggetti sottoposti a profilassi a lungo termine con lanadelumab. Per l'analisi dei costi e dei consumi, invece, la valutazione è stata limitata al primo anno di follow-up per tutti i pazienti, al fine di garantire l'omogeneità dei risultati. Inoltre, tra i pazienti con AEE inclusi nello studio, sono stati identificati coloro che avevano ricevuto almeno una prescrizione di lanadelumab durante tutto il periodo di disponibilità dei dati. Tali pazienti sono stati inclusi in una sotto-coorte di analisi, per la quale è stata considerata come data-indice la prima prescrizione di lanadelumab.

Caratteristiche demografiche e cliniche al baseline

Alla data-indice sono state analizzate le variabili demografiche (età e sesso) in tutti i pazienti con AEE e nel gruppo dei pazienti trattati con lanadelumab. Durante il periodo di caratterizzazione, è stato calcolato il Charlson Comorbidity Index (CCI) (10), che assegna un punteggio per specifiche comorbilità, ricercate nell'anno prima della data-indice attraverso farmaci e ricoveri. Nello specifico, il CCI quantifica il carico di comorbilità con pesi assegnati a condizioni di varia gravità: 1 punto per patologie cardiovascolari, respiratorie e neurologiche; 2 punti per diabete con danno d'organo, emiplegia, IRC, tumori non metastatici, leucemie e linfomi; 3 punti per epatopatia grave; 6 punti per metastasi e HIV/AIDS. La somma stratifica il rischio di mortalità. Inoltre, nel periodo di caratterizzazione sono stati raccolti i dati relativi alle condizioni e ai trattamenti farmacologici più comunemente descritti per i pazienti affetti da AEE: (a) ipertensione, identificata mediante almeno una prescrizione di farmaci antipertensivi (ATC C02, C03; C07; C08; C09) oppure almeno un ricovero con diagnosi di dimissione per ipertensione con codice ICD-9-CM 401 oppure un codice di esenzione A31; (b) ipercolesterolemia, identificata mediante almeno una prescrizione di farmaci ipolipemizzanti (ATC C10) oppure almeno un ricovero con diagnosi di dimissione per ipertensione con codice ICD-9-CM 272.0; (c) disturbi gastrointestinali (almeno 1 prescrizione di farmaci per disturbi gastrointestinali con codici ATC A02-04, A06, A07, A09); (d) depressione (almeno 1 prescrizione di farmaci antidepressivi con codice ATC N06A). I 10 farmaci più frequentemente prescritti per condizioni cliniche diverse dall'AEE sono stati riportati al secondo livello dei codici ATC.

Analisi del percorso terapeutico

Alla data-indice e durante il periodo di follow-up, sono state valutate le prescrizioni delle seguenti terapie in tutti i pazienti con AEE inclusi: i) C1-INH per via sia endovenosa (EV-C1-INH) sia sottocutanea (SC-C1-INH); ii) icatibant; iii) lanadelumab; iv) acido tranexamico per via orale; v) danazolo per via orale. In base alle loro indicazioni, le terapie sono state raggruppate tra farmaci per il trattamento acuto (EV-C1-INH, icatibant) e farmaci per la profilassi (SC-C1-INH, EV-C1-INH, lanadelumab, danazolo e acido tranexamico). Dal momento che gli EV-C1-INH possono essere utilizzati sia come trattamento acuto che per la profilassi, il farmaco è stato considerato come trattamento di profilassi, quando ne sia stato rilevato un uso continuativo (almeno 10 prescrizioni).

Inoltre, per i pazienti in trattamento con lanadelumab, è stato valutato il passaggio da un regime di dosaggio di 2 settimane a uno di 4 settimane. Dall'inizio della terapia, i pazienti sono stati monitorati per l'intero periodo di follow-up disponibile. Per determinare il regime di dosaggio, è stata utilizzata una proxy che classificava come regime di 2 settimane gli intervalli tra le dosi inferiori a 21 giorni e come regime di 4 settimane gli intervalli tra le dosi compresi tra i 21 e i 35 giorni.

Analisi dei consumi sanitari e dei costi diretti sostenuti dal SSN

L'utilizzo delle risorse sanitarie per paziente è stato valutato a un anno di follow-up sulla base del numero di trattamenti farmacologici totali, ricoveri ospedalieri, servizi ambulatoriali/test diagnostici e visite specialistiche per paziente. Per i costi è stata condotta un'analisi focalizzata sui pazienti trattati con lanadelumab. I database amministrativi sono stati utilizzati per l'estrazione del costo medio associato a una singola iniezione di lanadelumab. A partire da questo dato, è stato stimato il costo annuale della terapia tenendo conto della distribuzione della popolazione che effettua lo switch tra i diversi regimi di dosaggio.

Analisi statistica

È stata condotta un'analisi statistica descrittiva. Le variabili continue sono presentate come media ± deviazione standard (DS), mentre quelle categoriche come numeri e percentuali. Tutte le analisi sono state eseguite utilizzando STATA SE, versione 17.0 (StataCorp LLC, College Station, TX, USA).

Risultati

Caratteristiche cliniche e demografiche

Da un campione di 9.491.577 assistiti di ASL distribuite sul territorio italiano, sono stati identificati 258 pazienti con AEE, pari a circa lo 0,003% della popolazione in studio. Di questi, 220 (85%) sono stati inclusi per la presenza di un trattamento specifico per l'AEE, mentre i rimanenti 38 pazienti sono stati inclusi per la presenza del codice di esenzione attivo. Le caratteristiche demografiche e cliniche alla data-indice dei 258 pazienti con AEE sono riportate nella Tabella 1. Il 41,1% era di sesso maschile e l'età media (±DS) al momento dell'inclusione era di 44,6 (±21,5) anni, con il 9,7% (N = 25) dei pazienti di età compresa tra 0 e 11 anni, il 5,0% (N = 13) tra i 12 e i 17 anni e l'85,3% (N = 220) di età adulta. Tra i 258 pazienti con AEE, è stata ricercata la presenza di almeno una prescrizione di lanadelumab durante l'intero periodo di studio. Per i pazienti trattati con questo farmaco, la data-indice è stata considerata come la data della prima prescrizione. La Tabella 2 riporta le caratteristiche basali dei pazienti con AEE trattati con lanadelumab (N = 39). Tra questi, il 30,8% era rappresentato da maschi, l'età media (±DS) al momento dell'inclusione era di 45,1 (±18,6) anni e la durata media (±DS) del follow-up era di 1,2 (±0,7) anni.

TABELLA 1 - Caratteristiche demografiche dei pazienti affetti da AEE

	Pazienti con AEE (N = 258)
Sesso maschile, N (%)	106 (41,1%)
Età alla data-indice, anni, media ± DS	44,6 ± 21,5
Gruppi di età	
0-11 anni, N (%)	25 (9,7%)
12-17 anni, N (%)	13 (5,0%)
≥ 18 anni, N (%)	220 (85,3%)
Pazienti con AEE farmacologicamente trattati, N (%)	220 (85%)

Abbreviazioni: AEE: angioedema ereditario; DS: deviazione standard.

TABELLA 2 - Caratteristiche demografiche dei pazienti affetti da AEE trattati con lanadelumab

	Pazienti trattati con lanadelumab (N = 39)
Sesso maschile, N (%)	12 (30,8%)
Età alla data-indice, anni, media ± DS	45,1 ± 18,6
Durata del periodo di follow-up, anni, media ± DS	1,2 ± 0,7

Abbreviazioni: AEE: angioedema ereditario; DS: deviazione standard.

Per la popolazione complessiva e stratificata per gruppi di età, lo stato clinico dei pazienti con AEE al momento dell'inclusione è stato analizzato ricercando le comorbilità più frequenti durante il periodo di caratterizzazione. Il profilo di comorbilità dei pazienti è stato descritto in base alla frequenza dei pazienti con CCI pari a 0, 1 e ≥ 2. Complessivamente, il 55,8% dei pazienti rientrava nella categoria con CCI pari a 0, di cui circa il 53,6% degli adulti, il 61,5% degli adolescenti (11-17 anni) e il 72,0% dei pazienti pediatrici (0-11 anni). Tra le condizioni comunemente associate all'AEE, i disturbi gastrointestinali hanno interessato il 32,6% dei pazienti, seguiti da ipertensione (28,7%), ipercolesterolemia (13,6%) e depressione (10,1%) (Tab. 3).

Analisi degli schemi terapeutici

Gli schemi di trattamento alla data-indice in tutti i pazienti trattati farmacologicamente per l'AEE (N = 220) e in quelli stratificati per età sono descritti nella Tabella 4. Alla data-indice, l'80% dei pazienti era in trattamento per attacchi acuti (58% con C1-INH; 42% con icatibant), mentre il restante 20% dei pazienti era in profilassi (72,7% con C1-INH; 20,5% con danazolo).

TABELLA 3 - Caratteristiche cliniche dei pazienti affetti da AEE, stratificate per fasce d'età

	Popolazione totale con AEE (N = 258)	Pazienti con AEE, 0–11 anni (N = 25)	Pazienti con AEE, 12–17 anni (N = 13)	Pazienti con AEE, ≥ 18 anni (N = 220)
Charlson index, media ± DS	0,7 ± 1,1	0,3 ± 0,6	0,6 ± 1,1	0,7 ± 1,1
Charlson index = 0, N (%)	144 (55,8%)	18 (72,0%)	8 (61,5%)	118 (53,6%)
Charlson index = 1, N (%)	77 (29,8%)	6 (24,0%)	4 (30,8%)	67 (30,5%)
Charlson index ≥ 2, N (%)	37 (14,3%)	< 4	< 4	35 (15,9%)
Comorbilità				
Ipertensione, N (%)	74 (28,7%)	NR	NR	72 (32,7%)
Ipercolesterolemia, N (%)	35 (13,6%)	–	–	35 (15,9%)
Disordini gastrointestinali, N (%)	84 (32,6%)	–	NR	83 (37,7%)
Depressione, N (%)	26 (10,1%)	–	NR	24 (10,9%)

Abbreviazioni: AEE: angioedema ereditario; DS: deviazione standard; NR: non riportato per data privacy (< 3 pazienti).

TABELLA 4 - Schemi di trattamento alla data-indice in tutti i pazienti con AEE e in quelli stratificati per età

	Popolazione totale con AEE (N = 220)	Pazienti con AEE, 0–11 anni (N = 21)	Pazienti con AEE, 12–17 anni (N = 13)	Pazienti con AEE, ≥ 18 anni (N = 186)
Trattamenti per gli attacchi acuti, N (%)	**176 (80,0%)**	15 (71,4%)	7 (53,8%)	154 (82,8%)
C1-INH, N (%)	102 (58,0%)	13 (86,7%)	6 (85,7%)	83 (53,9%)
Icatibant, N (%)	74 (42,0%)	NR	NR	71 (46,1%)
Trattamenti per la profilassi, N (%)	**44 (20,0%)**	6 (28,6%)	6 (46,2%)	32 (17,2%)
Acido tranexamico (orale), N (%)	NR	–	–	NR
Danazolo, N (%)	9 (20,5%)	–	–	9 (28,1%)
C1-INH, N (%)	32 (72,7%)	6 (100,0%)	6 (100,0%)	20 (62,5%)

Abbreviazioni: AEE: angioedema ereditario; C1-INH: inibitori dell'esterasi C1; NR: non riportato per data privacy (< 3 pazienti).

Nei pazienti trattati in profilassi a lungo termine con lanadelumab (N = 39), l'analisi sui regimi di dosaggio ha mostrato che l'85% dei pazienti (33 su 39) ha iniziato il trattamento con uno schema di trattamento ogni 2 settimane. Tra questi 33 pazienti, il 75,8% (25 su 33) è passato successivamente a un regime di dosaggio di 4 settimane. In media (±DS), questa transizione è avvenuta dopo circa 4,1 (±2,7) mesi dall'inizio del trattamento con lanadelumab.

Consumi di risorse sanitarie e costi diretti per il SSN

L'analisi del consumo di risorse sanitarie è stata condotta durante i 12 mesi dopo la data-indice sui pazienti trattati per gli attacchi acuti (N = 171), sul totale dei pazienti in profilassi (N = 44) e sui pazienti in profilassi trattati con lanadelumab (N = 21) (Tab. 5). Nella popolazione trattata per attacchi acuti, il numero medio (±DS) di prescrizioni di farmaci per paziente è stato di 11,5 (±10,4). I pazienti in profilassi hanno mostrato un numero medio (±DS) più elevato di prescrizioni, pari a 16,2 (±12,0). La popolazione trattata con lanadelumab (N = 21) ha avuto il numero medio (±DS) più alto di prescrizioni, con 20,2 (±11,1). Per quanto riguarda i ricoveri, sia i pazienti trattati per attacchi acuti che quelli in profilassi hanno registrato una media di 0,2 ricoveri per paziente (DS = 0,5 e DS = 0,4, rispettivamente). Nella popolazione trattata con lanadelumab non sono stati riscontrati ricoveri durante l'anno successivo alla data-indice. In termini di servizi specialistici ambulatoriali, i pazienti trattati per attacchi acuti hanno avuto una media (±DS) di 3,7 (±5,8) visite per paziente, mentre quelli in profilassi hanno registrato una media (±DS) di 4,8 (±9,5) visite. La popolazione trattata con lanadelumab ha mostrato, invece, un numero medio (±DS) di 7,1 (±12,6) visite per paziente.

Limitatamente ai pazienti trattati con lanadelumab, è stato estratto dal database amministrativo il costo medio di una singola iniezione del farmaco. Sulla base di tali dati, è stato stimato che il costo annuale della terapia, considerando la distribuzione della popolazione che effettua lo switch tra i diversi regimi di dosaggio, ammonta a circa € 114.362.

TABELLA 5 - Consumo medio annuo di risorse sanitarie durante il primo anno di follow-up nei pazienti con AEE trattati

	Popolazione con AEE trattata per attacchi acuti (N = 171)	Popolazione con AEE trattata in profilassi (N = 44)	Popolazione con AEE in profilassi con lanadelumab (N = 21)
N. prescrizioni di farmaci, media ± DS	11,5 ± 10,4	16,2 ± 12,0	20,2 ± 11,1
N. ricoveri per tutte le cause, media ± DS	0,2 ± 0,5	0,2 ± 0,4	–
N. servizi specialistici ambulatoriali, media ± DS	3,7 ± 5,8	4,8 ± 9,5	7,1 ± 12,6

Abbreviazioni: AEE: angioedema ereditario; DS: deviazione standard.

Discussione

La presente analisi ha considerato una popolazione di pazienti affetti da AEE di tutte le età, descrivendo i percorsi terapeutici durante la profilassi e gli attacchi acuti e concentrandosi sull'utilizzo dei farmaci recentemente immessi in commercio, in particolare il lanadelumab utilizzato nella profilassi a lungo termine.

La popolazione dello studio era composta soprattutto da adulti, con una percentuale minore di pazienti pediatrici e adolescenti. Non è stato possibile valutare la rappresentatività delle diverse sottocategorie di AEE (tipo I, II e III) poiché la metodologia di identificazione dei pazienti è basata su codici di esenzione e trattamenti specifici, che non permettono di discriminare tra le varie forme della malattia (1). Le caratteristiche demografiche sono coerenti con recenti analisi retrospettive condotte sulla popolazione italiana, secondo le quali il 43-47% dei pazienti con AEE è di sesso maschile, con un'età media di 44-45 anni (4,9). Tra i pazienti che hanno iniziato il trattamento con lanadelumab in profilassi, si è invece osservata una minore prevalenza di individui di sesso maschile (30,8%), con un'età media al momento dell'inclusione in linea con quella della popolazione generale con AEE (45,1 anni) e con i dati della letteratura (11).

Analizzando le caratteristiche cliniche dei pazienti con AEE, non sorprende che il profilo di comorbilità sia meno grave nei pazienti più giovani, come documentato dalla maggiore proporzione di soggetti di età inferiore ai 18 anni nella categoria con CCI pari a 0.

Tra le condizioni concomitanti, i disturbi gastrointestinali sono risultati i più frequenti, essendo stati osservati in circa un terzo della coorte di pazienti con AEE, in linea con i dati presenti in letteratura. Uno studio italiano basato su dati amministrativi ha riportato una prevalenza del 36,5% di disturbi gastrointestinali nei pazienti con AEE, sottolineando come questi sintomi siano spesso correlati agli attacchi addominali legati all'edema del tratto gastrointestinale (9).

Anche l'ipertensione e l'ipercolesterolemia erano presenti in una quota significativa di pazienti con AEE, rispettivamente pari al 28,7% e al 13,6% dei casi. È possibile che questa associazione sia dovuta all'effetto degli androgeni attenuati, come il danazolo, il cui coinvolgimento nello sviluppo di queste comorbidità è stato dimostrato da studi recenti (12).

Infine, la depressione, presente nel 10,1% dei nostri pazienti, rappresenta una comorbilità di particolare rilevanza, considerando l'impatto psicosociale dell'AEE. Diversi studi hanno dimostrato una prevalenza elevata di disturbi dell'umore in questi pazienti, spesso legati alla natura imprevedibile e invalidante della malattia (13).

Nel complesso, la frequenza di comorbilità osservate rafforza l'idea che la gestione dell'AEE debba essere multidisciplinare, includendo non solo il controllo degli attacchi acuti e la profilassi, ma anche il monitoraggio e il trattamento delle condizioni associate, al fine di migliorare la qualità della vita e di ridurre il carico complessivo della malattia.

L'analisi degli schemi di trattamento ha rivelato che circa l'80% dei pazienti era in trattamento per attacchi acuti, mentre il restante 20% era in profilassi al momento dell'inclusione nello studio. I farmaci prescritti per gli attacchi acuti sono stati

icatibant (42%) e i derivati del C1-INH (58%), questi ultimi usati anche in profilassi (72,7%). Solo 6 pazienti sono risultati in profilassi con il danazolo. L'assenza di pazienti trattati con acido tranexamico risulta conforme alle attuali Linee Guida, sottolineando l'aderenza agli approcci terapeutici raccomandati (5).

Per i pazienti che hanno iniziato il trattamento con lanadelumab in profilassi, è stato valutato il passaggio da un regime di dosaggio ogni 2 settimane a uno ogni 4 settimane. Nell'analisi è emerso che la maggior parte dei pazienti (81%) che inizia con un regime di trattamento bisettimanale passa a un regime di dosaggio ogni 4 settimane dopo circa 4 mesi dall'inizio del trattamento. La possibilità di estendere l'intervallo tra le iniezioni di lanadelumab offre non solo una maggiore flessibilità nel piano terapeutico, ma anche importanti implicazioni in termini di gestione clinica, di ottimizzazione delle risorse e di qualità della vita dei pazienti.

L'analisi sui consumi sanitari evidenzia un maggiore consumo di risorse tra i pazienti trattati con lanadelumab, in termini di prescrizioni e di servizi specialistici ambulatoriali, che tra i pazienti trattati con altre terapie. Questo potrebbe essere imputabile a un maggiore controllo da parte degli specialisti nelle fasi iniziali del trattamento, per valutare la possibilità di estendere l'intervallo tra le iniezioni. Al contrario, l'assenza di ricoveri nell'anno successivo all'inizio del trattamento con lanadelumab potrebbe suggerire un potenziale beneficio clinico associato a questo farmaco. Sarà necessario approfondire la comprensione di questo fenomeno mediante ulteriori ricerche volte a esplorare gli effetti a lungo termine del lanadelumab sulla gestione clinica dell'AEE.

I risultati ottenuti dalla presente analisi devono essere interpretati alla luce di alcuni limiti, dovuti alla natura osservazionale dello studio basato sui database amministrativi. Un limite è rappresentato dalla mancanza di informazioni cliniche riguardanti la severità e lo stato della patologia e da altri possibili fattori confondenti che potrebbero aver influenzato i risultati. A questo proposito, dato che la popolazione è stata identificata attraverso i codici di esenzione attivi, le prescrizioni di farmaci e le diagnosi di dimissione ospedaliera come proxy di diagnosi di AEE, alcuni pazienti non trattati e non ospedalizzati potrebbero non essere stati individuati. Inoltre, l'identificazione dell'uso profilattico di EV-C1-INH sulla base di ≥ 10 prescrizioni consecutive rappresenta una semplificazione basata su un criterio operativo per distinguere l'uso cronico (potenzialmente profilattico) da quello episodico per il trattamento acuto, anche se tale criterio non è supportato da evidenze cliniche dirette.

Tuttavia, i database amministrativi, grazie all'elevata disponibilità di dati con aggiornamenti periodici, sono una fonte sempre più utilizzata per la ricerca sanitaria. Gli studi basati su dati di real-world possono infatti rappresentare un importante supporto per una migliore comprensione del decorso clinico e della gestione dei pazienti, soprattutto nei casi di malattie rare, dove le basse dimensioni del campione sono spesso un problema sostanziale per gli studi clinici.

Conclusioni

Questo studio ha fornito una descrizione approfondita dei pazienti con AEE e della loro gestione terapeutica nella pratica clinica italiana. Inoltre, nonostante il numero limitato di pazienti in terapia con lanadelumab, è stato possibile evidenziare preliminarmente come lanadelumab stia emergendo tra i trattamenti per l'AEE in Italia. In particolare, si è osservato come la maggior parte dei pazienti che avevano ricevuto lanadelumab abbia potuto beneficiare di una somministrazione ogni 4 settimane, suggerendo un buon controllo della malattia. Tuttavia, sarebbe importante condurre ulteriori studi includendo una popolazione più ampia di pazienti e analizzando la popolazione adulta per macro-fasce d'età tra i 18 e i 64 anni e ≥ 65 anni, con un follow-up più esteso per valutare tali risultati anche in termini di effetti clinici nel lungo periodo.

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ORIGINAL RESEARCH ARTICLE

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Effectiveness study of the recombinant enzymes pbserum HIGH in the treatment of pathological scars: a pilot study

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ABSTRACT

Introduction: Pathological scars, despite the achievements of modern medicine, are still a problem. Its prevalence can reach up to 50% in emergency surgeries. These scars can lead to physical complications, including impaired mobility, altered sensation, and discoloration, and may even cause pain. In this study, we explore the possibilities of using the combined drug of recombinant collagenase and lyase enzymes, and high molecular weight hyaluronic acid (HMWHA) pbserum HIGH in the treatment of pathological scars.
Methods: patients of the main group received a course of intra-cicatricial injections of the drug, treatment results were assessed clinically, according to the Vancouver Scar Scale (VSS) and Observer Scar Assessment Scale (POSAS) scales, the results were compared morphologically with standard scars treatment methods (biopsies were taken before and after treatment).
Results: Clinically, patients of the main group received a pronounced positive transformation of scar tissue in 6 weeks, statistical processing of data confirms the reliability of changes, morphological studies prove the normotrophic nature of the changes in the scars (including comparison with the control group).
Conclusions: Remedy of recombinant collagenase and lyase enzymes in combination with HMWHA pbserum HIGH in the form of the course of intra-cicatricial injections is a safe and effective method of treating pathological scars.

Keywords: Collagenase, Hyaluronic acid, Lyase, Programed scar remodeling, Recombinant enzymes, Scars

Introduction

The treatment and prevention of pathological scarring remains a pressing issue in all areas of medicine. Epidemiological studies estimate that the prevalence of hypertrophic scars ranges from 32 to 72% (1), whereas keloids affect between 4.5 and 16% of the general population (2), with a higher prevalence among individuals of African, Asian, or Hispanic descent. The condition affects both sexes equally, with the highest incidence occurring during the second and third decades of life (3,4) and in 8-67 % of burn convalescents (5). The etiopathogenesis of pathological scarring is well-studied, but clinical dissatisfaction with the treatment outcomes persists. Scar tissue can only be completely removed through surgical treatment, which involves scar excision and the replacement of the wound defect with a healthy skin flap. However, this is not always possible due to the scar's location, area, and type. Patients may also not be ready for surgery (e.g., young children). Therefore, in most cases, the specialist's objective is to make the scars as invisible as possible on the patient's body, both visually and subjectively. Today, various physiotherapy protocols and instrumental techniques, as well as steroid hormone injections, are actively used (6-12).

Previous scientific, clinical, and morphological studies of the effectiveness of injectable scar treatment methods have contributed to the development of the Programed Pathological Scar Remodeling protocol by the authors of this article (8,13,14). The main concept of the method is to inject several groups of drugs that normalise the functional characteristics of the extracellular matrix in scar tissue, leading to its remodeling (not destruction!) and the formation of more normotrophic tissue. When this method is combined with continuous elastic compression, patients achieve satisfactory results in a relatively short period of time (8,13,14). This protocol is especially important for preventing pathological scarring in patients undergoing surgical treatment for scarring pathology, as well as in the field of reconstructive plastic surgery in general, when the drugs specified in the protocol are injected during the immediate post-operative period (14,15). This approach aims to optimise conditions in the extracellular matrix of the surgical wound for the formation of a normotrophic post-operative scar (14,15).

The subject of this study was to investigate the mechanisms and results of the targeted action of recombinant collagenase and lyase enzymes and high molecular weight hyaluronic acid (HMWHA) in pbserum HA 1.5 HIGH (Proteos

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Biotech, S.L., Spain) on the formation or transformation of scar tissue via intra-cicatricial injection. The drug was chosen based on the widely studied mechanisms of action of collagenase. Recombinant collagenases target abnormal collagen accumulation, breaking it down enzymatically. These enzymes cleave triple-helical collagen at multiple sites, aiding in ECM degradation. Approved previously for Dupuytren's and Peyronie's diseases and the Edematous-fibrosclerotic panniculopathy, also called cellulitis (16,17). Across these clinical applications, the enzyme has consistently shown a favorable safety profile and encouraging therapeutic outcomes (16,17). Another interesting enzyme, lyase (a type of hyaluronidase, a depolymerizer), which provides conditions for collagenase activity and removes degradation products; promotes the reduction in the viscosity of biological fluids, increasing vascular permeability and accessibility of other active compounds at the application site, promotes fluid drainage from the ECM—thus reducing edema—and modulates the inflammatory response (18). Lipase function is to catalyze the reversible hydrolysis of triglycerides from adipocytes embedded in fibrotic tissue into glycerol and free fatty acids, enhancing mechanical pliability. In humans, lipase activity is regulated by hormonal factors (such as insulin), dietary habits, and physical activity, influencing both lipogenesis and lipolysis (17,19). High molecular weight (>400 kDa) hyaluronic acid (HMWHA) is more than just a volumizing molecule. It hydrates tissues, facilitates enzyme diffusion across the extracellular matrix, and acts as a physical barrier that helps modulate inflammatory responses. It also acts as a mechanical barrier (anti-adhesive gel), facilitating debridement in hypertrophic scars. Moreover, hyaluronic acid is not just a passive vehicle; it's an active player in the wound healing cascade. It inhibits the upregulation of TGF-β, a key driver of fibrosis. Unlike low-molecular-weight HA, HMWHA decreases fibroblast hyperproliferation (20), been considered as an ECM modulator (21,22).

The technology of recombinant enzyme production minimises the risk of immunological incompatibility, i.e., allergic reactions, while maintaining enzyme properties and activity identical to human characteristics.

We define two objectives: (i) to evaluate the drug's clinical effectiveness at various stages of scar tissue formation (including comparison with standard treatment); (ii) to examine the morphological changes in tissues (including comparison with standard treatment).

Materials and methods

In 2016-2017, the Burn Centre in Kharkiv City treated 15 patients with pathological scars of varying duration, including women and men aged 18-54. These patients were the main study group and received the presented scar treatment protocol (Table 1). The scar aetiology in the main group was 11 post-burn patients, four post-operatives. The results of the treatment were compared with a control group of 15 patients from previous studies on the treatment of scars conducted by the author (8,13,14). Patients in both groups had scars of two types: atrophic and hypertrophic (Table 1). The study has been performed in accordance with the Declaration of Helsinki and approved by an ethics committee.

All the patients in the main group received intra-cicatricial injections at 2-week intervals for a total of 6 sessions. A unit of Pbserum HA 1.5 HIGH (Proteos Biotech, S.L., Spain) was applied in each session. It consisted of a vial containing a cocktail of recombinant enzymes—collagenase, lipase, and lyase—reconstituted with 2 mL of HMWHA and 3-10 mL of 0.9% sodium chloride (NaCl) solution, depending on the scarred area. Additionally, 0.5 mL of a 2% lidocaine solution was added. Injections of 0.5 cc per point were administered into the scar tissue using a 27G needle, employing either a retrograde linear or multipuncture technique. The patients completed the POSAS table before each session and at the end of the treatment course to subjectively assess the characteristics of their scars, including pain and itching, thickness, difference from surrounding tissues, and colour. At the same time, a doctor who was not involved in patient treatment completed the Vancouver Scar Scale (VSS) tables to objectively assess scar tissue characteristics, such as autonomic response, pliability, height above the skin level, and pigmentation, before each session and at the end of the treatment course. In addition, in patients with hypertrophic scars, a biopsy was performed to the full depth of the scar in a specific area before the start of the treatment course, and the same area was re-sampled 6 months later at the end of treatment. The microscopic specimens were stained with hematoxylin-eosin, Van Gieson's picrofuchsin (for collagen), Einarson's gallocyanine-chrome alum (for total nucleic acids), and the PAS reaction was carried out. Microscopy was done with an Axiostar-plus microscope (Zeiss, Germany). Photocontrol was carried out at all stages of treatment.

TABLE 1 - Patient groups

Diagnosis	Main group, people (%)	Control group, people (%)
Atrophic scars	4	5
Hypertrophic scars	11	10
Total	15	15

Treatment outcomes were assessed using PSOAS for subjective observation results; objective VSS before treatment, before each procedure, and after treatment; morphological examination of hypertrophic scar biopsy specimens before and after treatment; comparative morphological examination of scar tissue biopsy specimens from patients in the control group and patients receiving standard treatment.

All results were statistically analyzed using the Statistica (StatSoft, Inc.) software.

Results

The clinical outcomes of the patients in the control group were used retrospectively, as the author's previous works demonstrated a significant difference in the timing and outcomes of treatment in favour of the Programmed Pathological Scar Remodeling protocol (8, 13-15); biopsy specimens for this morphological study were obtained in a remote period of time. The statistical analysis of the data for both scales revealed a statistically significant difference before and after treatment (Tables 2 and 3).

TABLE 2 - Treatment outcomes according to the VSS scale: changes in %

Types of scars	Autonomic response, %	Pigmentation, %	Pliability, %	Scar height, %
Hypertrophic scars	–81.3 ± 3.12	–38.7 ± 0.84	–19.9 ± 0.38	–60.3 ± 2.1
Atrophic scars	+78.8 ± 2.49	+62.1 ± 1.29	+38.6 ± 0.95	+78.9 ± 2.93

TABLE 3 - Treatment outcomes according to the PSOAS scale: changes in %

Types of scars	Pain, %	Itching, %	Pigmentation, %	Pliability, %	Relief, %
Hypertrophic scars	63.4 ± 2.12	68.2 ± 1.27	58.3 ± 0.76	58.7 ± 1.15	70.1 ± 1.84
Atrophic scars	50 .9 ± 1.94	71.2 ± 1.44	39.1 ± 0.36	54.5 ± 1.08	62.5 ± 0.97

All patients showed clinical improvement after the first treatment session, with more pronounced outcomes at the end of the treatment course. Importantly, the changes intensified within a few months after completion of the treatment course. In patients with hypertrophic scars, softening of the scars, reduction in the height of the scars above the healthy skin, lightening, decrease in epidermal peeling, and decrease in the intensity of the autonomic response were observed, and the scar tissue could be pinched. Subjectively, there was a decrease in pain and itching; the tissues became softer, more elastic, and lighter (Figs 1 and 2). In patients with atrophic scars, volume filling and smoothing in height compared to healthy skin were observed, as well as a decrease in the brightness of the vascular pattern and a change in the colour of the scar tissue to more flesh-like. In general, the scars became less visible (Fig. 3). No local or systemic adverse effects of the drug were observed during the treatment. During this time, the patients received no additional anti-scarring therapy.

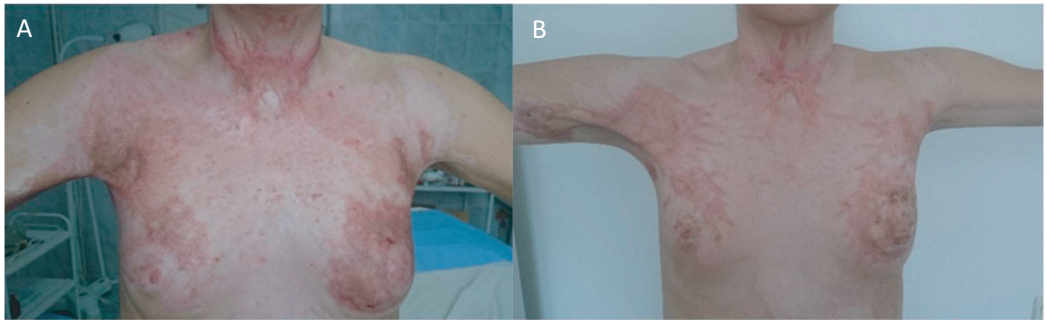

FIGURE 1 - Patient 18 years old, post-burn hypertrophic scars, main group. A) before treatment. B) after treatment.

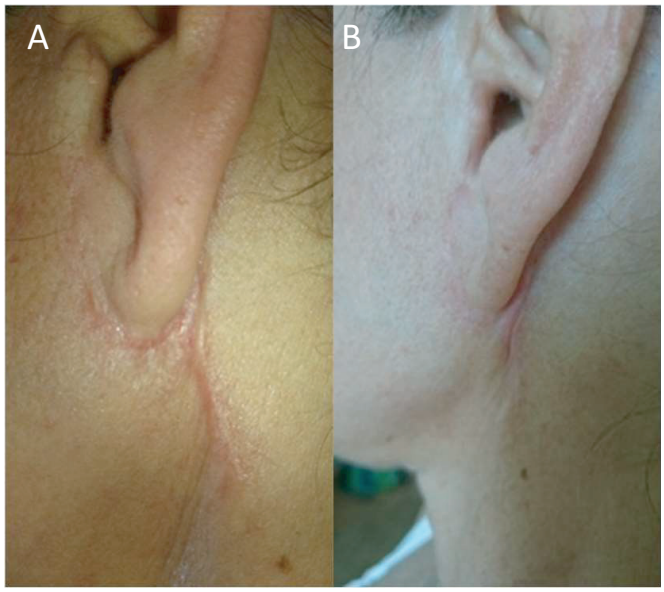

FIGURE 2 - Patient 54 years old, post-operative hypertrophic scars on the face, main group. A) before treatment. B) after treatment.

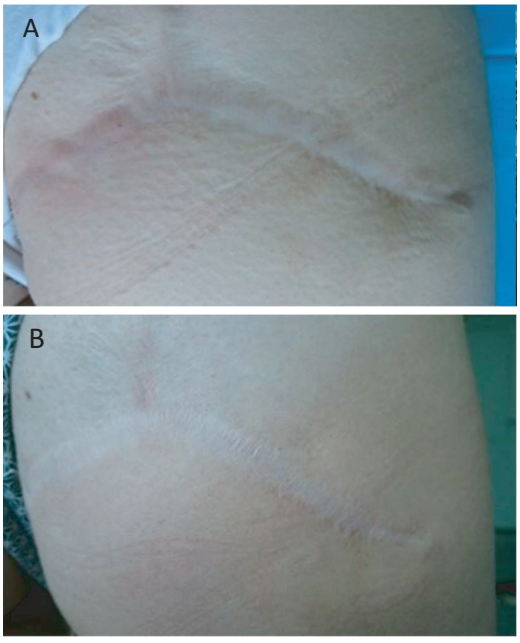

FIGURE 3 - Patient 22 years old, post-operative atrophic scars on the right buttock, main group. A) before treatment. B) 2 months after treatment.

Morphological examination

In patients with hypertrophic post-burn scars in the main group, numerous fibroblasts with very high morphological and functional activity were observed under the microscope before treatment, both in the depth of the scar and in the subepidermal layer. The optical density of fibroblast nuclei when stained by Einarson is 0.187 + 0.009 conventional units of optical density. Collagen was typically represented by thin, tortuous fibers, but in some cases, its compaction, similar to homogenization, was already visible. The presence of inflammatory infiltrate foci (lymphocytes, macrophages) in the scar tissue is noteworthy, with a decrease in collagen fiber density in these areas. The epidermis was thick, lacked a basement membrane, and had hyperproliferation of epidermocytes in the basal and lower prickle cell layers. Patients in the main and control groups showed a decrease in fibroblasts and an increase in fibrocytes in the scar depth 6 months or more after injury, indicating a slowdown in protein synthesis processes. However, the situation was reversed in the subepidermal layer. During standard treatment, a very large amount of collagen was accumulated in the upper layers of the scar tissue, which was so densely packed that it appeared homogeneous. Clinically, this is manifested as a dense, inelastic, and uneven scar. Active fibroblasts were also present, as were small numbers of diffusely distributed macrophages and lymphocytes. At the same time, the depth of the scar is dominated by fibrocytes, which are inactive in the function of protein synthesis, and this is also combined with the dissociated arrangement of collagen fibers. The optical density of fibroblast cells when stained according to Einarson is 0.142 + 0.006 conventional units of optical density - that is, the nuclei of fibroblasts are more euchromic. The proposed treatment reduced the number of fibroblasts and the accumulated collagen in the subepidermal layers. In addition, hyperproliferation in the basal cell layer was virtually eliminated, and the epidermis thinned, without the formation of acanthosis or papillomatosis (Figs 4A and B; Figs 5A and B).

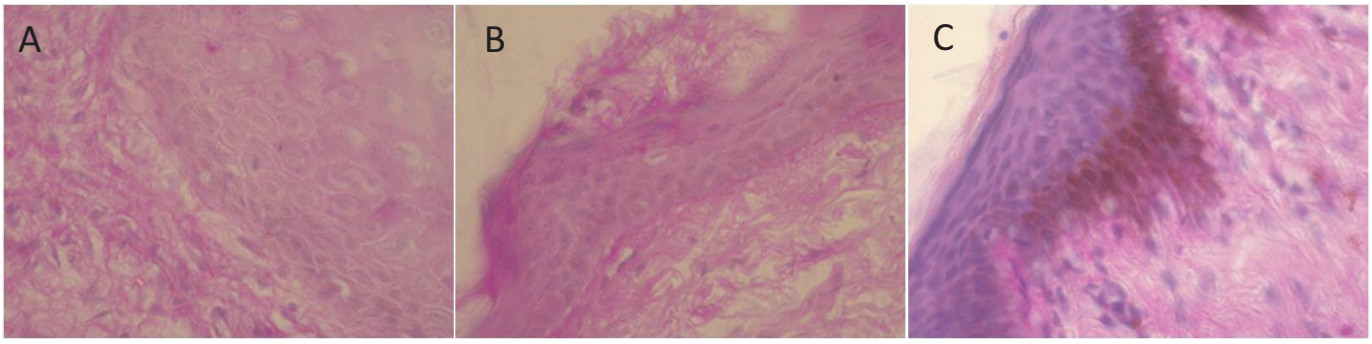

FIGURE 4 - PAS reaction, 400× magnification. A) post-burn hypertrophic scar on the torso prior to treatment, main group. An area of the epidermis with no basement membrane. B) post-burn hypertrophic scar on the torso 6 months after treatment, main group. The epidermis is thin, the keratin layer has thickened, and the basal cell layer does not show any signs of hyperproliferation. The epidermis's lower edge is smooth, and the formation of the basement membrane is visible. C) post-burn hypertrophic scar after treatment, control group. Melanin hyperproduction; absence of epidermal basement membrane.

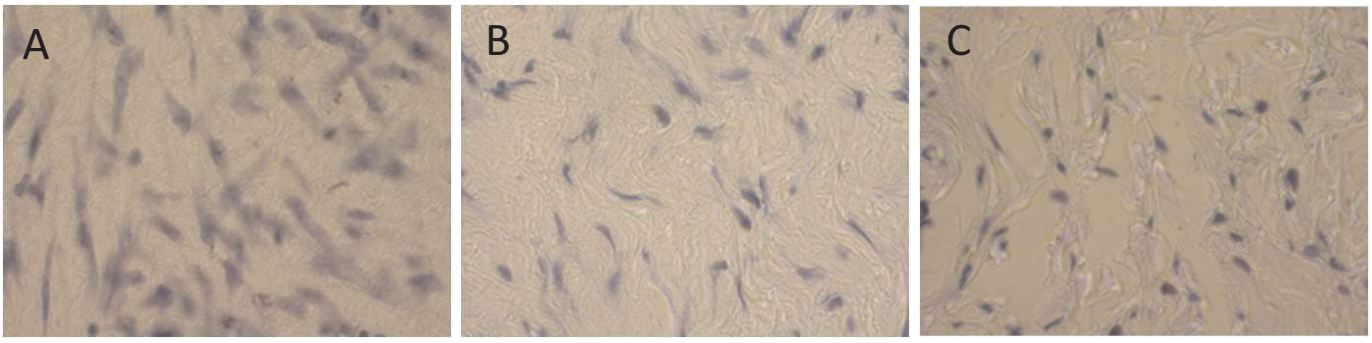

FIGURE 5 - Einarson staining, 400x magnification. A) post-burn hypertrophic scar on the torso prior to treatment, main group. The deeper layers of scar tissue contain numerous morphologically and functionally highly active fibroblasts (large volume of cytoplasm with high RNA content). B) post-burn hypertrophic scar on the torso 6 months after treatment, main group. In the scar's deeper layers, many fibroblasts lost their protein-synthesising activity and transformed into fibrocytes. C) post-burn hypertrophic scar after treatment, control group. Cellular elements of the deeper layers of the scar include both small fibroblasts with a low volume of cytoplasm and fibrocytes.

In the main group, a second biopsy specimen was taken 6 months after the first sampling, when the proposed treatment course was administered. As previously stated, the number of fibroblasts and accumulated collagen decreased not only in the depth of scars, but also in the subepidermal layers. This suggests a low level of ECM activity in terms of uncontrolled synthesis of cellular and fibrous elements. There were few lymphocytes and macrophages, indicating

that there was no inflammatory reaction associated with active pathological scarring. In addition, hyperproliferation in the basal cell layer of epidermis was virtually eliminated, the basement membrane was forming, and the epidermis thinned, with no acanthosis or papillomatosis. The formation of the basement membrane of the epidermis indicates the production of type IV collagen, the main function of which is to support tissues in the process of remodeling and regeneration (after the embryonic period). The examination of biopsy specimens from patients in the control group after standard therapy revealed the following: most microscopic specimens lacked a basement membrane, had epidermal areas with a papillomatous surface, and exhibited increased keratinization; in another part of the biopsy specimens, the epidermocytes of the basal cell layer had a vertical, sharply elongated shape due to hyperproliferation. In all cases, the epidermis produced an excessive amount of melanin. Protrusions and depressions formed on the surface of the scars (Fig. 4C, Fig. 5C). Such characteristics of the epidermal layer, particularly the basement membrane, differ significantly from those of the main group, indicating that non-physiological parameters of ECM function are preserved in the scar area in patients receiving standard therapy. The superficial subepidermal layer is uniformly fuchsinophilic, or there is significant fuchsinophilia, indicating excessive interstitial collagen accumulation with the formation of thick bundles and homogeneous areas. Cellular elements of the deeper layers of the scar include both small fibroblasts with a low volume of cytoplasm and fibrocytes. These morphological characteristics also suggest that the standard therapy does not create new, more physiological conditions in scar tissue, but, on the contrary, it preserves pathological parameters, though without pronounced activity (Fig. 5).

Discussion

The clinical outcomes of using a combined drug of recombinant collagenase, lipase, and lyase enzymes with HMWHA in the form of a course of intra-cicatricial injections demonstrated high effectiveness, as evidenced by objective and subjective observations. No complications or adverse events were observed during the treatment. A multicenter study involving 44 patients found that the enzymatic cocktail pbserum HA 1.5 High significantly reduced pruritus, pain, thickness, irregularities, and stiffness in hypertrophic, atrophic, and keloid scars from the very first application (23). The treatment showed excellent results across all evaluated parameters, with most patients experiencing noticeable improvement after just one session. The findings highlighted a clear antifibrotic effect, supporting its potential as a promising therapeutic option for scar management.

Importantly, the treatment demonstrated a strong safety profile. Adverse effects were generally mild and self-limiting, including erythema, swelling, injection site pain, and bruising, all of which responded well to standard pain relief. While 27% of patients experienced a single adverse event, 68% reported multiple symptoms. Notably, 93% of these effects were mild, and no serious adverse events were reported. Pain was the most commonly reported symptom, affecting 91% of participants, and local reactions such as edema, erythema, and bruising occurred in 75% of cases. All adverse events resolved within 48 hours, and no patient discontinued treatment due to side effects (23).

Morphological examination of the scar tissue before and after the proposed treatment revealed that all elements of hypertrophic scar tissue, as well as the epidermis that covers it, showed signs of inhibition of the processes that cause scar hypertrophy. A comparison of the morphological characteristics of the scars after treatment to those of patients in the control group demonstrated a significant difference in the quality and quantity of cellular and fibrous structures of the dermal extracellular matrix. Particularly noteworthy is the formation of the basement membrane and the normotrophic remodeling of the epidermal layers, which is clinically manifested by an improvement in the colour and microrelief of the scars—a reduction in the hyperpigmentation of hypertrophic scars and a brighter colour of atrophic scars, smoothness, and a decrease in itching and peeling. This remodeling is possible, in part, by the production of type IV collagen. It can be concluded that the proposed therapy has a direct effect on the functions and properties of the ECM in the area of the pathological scar, promoting their return to natural and physiological parameters. Structural changes in the subepidermal layers differ between the main and control groups, with cellular elements showing less pathological activity and collagen synthesis processes returning to normal. This clearly demonstrates the benefits of the presented treatment.

By directly breaking down ECM components and modulating inflammatory responses, this approach offers a rational, substrate-specific alternative to conventional therapies. When combined with HMW-HA, which supports tissue hydration and regulates inflammation, enzyme therapy not only promotes ECM remodeling but also facilitates tissue regeneration.

The use of multi-component enzymatic formulations opens new possibilities for maximizing therapeutic outcomes. Emerging clinical and experimental evidence suggests that these enzymatic cocktails may redefine the standard of care for pathological fibrotic scars. As research advances, the application of this synergistic therapy is expected to broaden into other fibrotic conditions, aligning treatment strategies more closely with the underlying pathophysiology.

As a limitation of the study, this patient series refers to patients admitted several years ago, and the therapeutic options might have changed in the meantime.

Conclusion

Therefore, the combination of recombinant collagenase, lipase, and lyase enzymes with HMWHA results in positive clinical outcomes based on the physiological remodeling of a pathological scar's ECM. More studies should be done to get more rigorous data.

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Authors' contributions

Dr. Korkunda has contributed to the clinical part, the analysis, and the writing. Gubina-Vakulyk has contributed to the morphological and immunohistochemical part. Dr. López Berroa has supported the protocol used for pbserum.

Disclosures

Conflicts of interest: Dr. Korkunda and Dr. Gubina-Vakulyk declare they do not have a conflict of interest. Dr. López-Berroa is an employee of Proteos Biotech.

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ERRATUM

Open Access

Erratum in "Sharing diagnostic and therapeutic pathways in pulmonary arterial hypertension: a Roadmap for the Triveneto region"

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In the article "Sharing Diagnostic and Therapeutic Pathways in Pulmonary Arterial Hypertension: A Roadmap for the Triveneto Region," (1) which appeared in Volume 12, Issue 1 of AboutOpen, translated tables 2 and 3 have been removed. They are available in their original format at the referenced source. We apologize for any inconvenience caused to the readers by these changes, which do not affect the final results of the study.

The final version of this article is available online and includes a reference to this correction.

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EDITORIAL

Open Access

Good clinical practice revision 3: evolution or revolution?

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The new ICH E6(R3) (1) Good Clinical Practice (GCP) guidelines represent the most significant update to GCP (2) since its inception more than 25 years ago. Published in its final version in January 2025, these guidelines introduce innovative provisions applicable to various types and contexts of clinical trials, ensuring the continued relevance of GCP in an era of rapid technological and methodological advancements. Specifically, the new version encourages a proportionate, risk-based approach to study conduct, promoting fit-for-purpose solutions. Additionally, it strengthens transparency through the public registration of trials and the dissemination of results, while providing further guidance to improve the informed consent process. The R3 update is a substantial shift from the R2 (3) addendum of 2016 (which introduced initial elements of a risk-based approach and electronic data management): the R3 revision fully embraces the new paradigms of clinical research, from quality by design to the use of digital technologies and decentralized trials, with a stronger focus on the patient.

From a structural perspective, R3 completely replaces the previous R2 version and redefines its architecture. The document is divided into General Principles (11 GCP principles) and specific annexes. Annex 1 applies to traditional interventional clinical trials (and includes practical appendices on Protocol, Investigator's Brochure, Essential Documents, etc.), while Annex 2 (4), not yet published in its final form, will provide additional considerations for non-traditional trials, such as pragmatic studies, decentralized studies, or those using real-world data.

This modularity is designed to keep GCP principles up-to-date as technologies, methods, and study designs evolve, allowing for streamlined and targeted updates through new annexes. Annex 2, in particular, will address innovative elements such as decentralized trials and the integration of Real World Data sources, ensuring that these approaches are also conducted in compliance with GCP principles and fit-for-purpose. The General Principles and Annex 1 will come into effect in July this year, while Annex 2, already under public consultation, will be finalized and made available later.

Risk-Based Approach and Quality Management

ICH E6(R3) builds on the foundation laid by ICH E8(R1) (General Considerations for Clinical Studies), promoting a culture of quality from the early stages of clinical development. The Quality by Design paradigm is emphasized: quality must be proactively designed into the study, planning from the outset how to prevent deviations that could affect critical data or participant safety. In this context, the new guideline requires the explicit identification of Critical-to-Quality (CtQ) factors for each trial, those aspects of design and conduct whose control is essential to protect participants and ensure the reliability of the data collected. Resources should be concentrated on these critical factors during study planning and management, dedicating proportionate attention to their importance and complexity.

The cornerstone principle of R3 is proportionality to risk: processes, control measures, and monitoring activities must be proportionate to the inherent risks for participants and the impact on critical study data. This extends and strengthens the risk-based approach introduced in R2, embracing a holistic view of risk management throughout the study lifecycle, from protocol design to final analysis. In practice, sponsors are encouraged to simplify where possible; operational procedures, data collection, and quality controls should focus on what is critical and avoid burdening the study with unnecessary complexity that does not add value to participant safety or result robustness. A careful evaluation of CtQ factors and associated risks allows for concentration on elements essential to the study's objectives, enhancing efficiency and effectiveness.

Operationally, the section on Quality Management has been expanded and clarified. Sponsors must establish a quality management system that includes preventive quality assurance (QA) and quality control (QC) processes, integrated into routine monitoring and study oversight activities. Additionally, the definition of "tolerance limits" for specific key study parameters (the so-called Quality Tolerance Limits

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introduced in R2) is clarified: R3 specifies that acceptable ranges should be established, beyond which deviations may indicate systemic problems to investigate and correct. In summary, the renewed GCP approach aims to design quality into clinical studies and proactively manage the most relevant risks, rather than simply reacting in a corrective manner. This shift in mindset is expected to result in leaner, more robust trials focused on the most impactful aspects of validity and safety.

Defined Roles and Responsibilities

The R3 revision dedicates one of its fundamental principles to clearly defining roles and responsibilities for all actors involved in the study. It is emphasized that the sponsor and the principal investigator retain ultimate responsibility for their respective activities, even when delegating tasks or functions to third parties. Each delegation of tasks must be documented in written agreements that clearly define roles, activities, and responsibilities. In other words, if the sponsor delegates tasks to a contract research organization (CRO) or other vendors, they remain responsible for the conduct of the study. They must ensure proper oversight of these delegated activities. Similarly, the investigator may delegate certain activities (e.g., to sub-investigators or study personnel) but retains direct responsibility and oversight for everything happening at the clinical site. E6(R3) emphasizes that the level of investigator supervision over delegated activities should be proportionate to their criticality and associated risks, applying the same risk-based logic to the management of the study team.

Terminologically, the new version introduces the concept of a "service provider" to refer to any individual or organization external to the sponsor or investigator that provides a service related to the clinical trial. This expands the scope compared to R2 (which mainly referred to Contract Research Organizations - CROs), acknowledging the variety of partners involved in modern trials: centralized laboratories, technology vendors, external committees, and other specialized services. R3 further clarifies that agreements with these service providers or external parties must be finalized before the study begins, clearly defining tasks and responsibilities. It also includes a specific mention of the need for the sponsor to extend its quality oversight to structures or activities outside the traditional experimental site: for example, centralized laboratories, imaging diagnostic services, or other vendors entrusted with study data must be integrated into the sponsor's quality assurance/quality control strategies. This is also reflected in the role of the Principal Investigator, who is required to extend oversight to any activities performed outside the experimental site (e.g., home nursing services). Ultimately, R3 emphasizes a more structured and transparent governance model: who does what in the clinical trial must be clear and documented, with the sponsor and investigators remaining responsible and actively involved in overseeing all delegated aspects of the trial. This helps avoid gaps in responsibility and ensures that the quality and integrity of the study are maintained throughout the operational chain.

Revised Essential Documentation

A significant change in R3 concerns the management of essential clinical trial documentation (formerly known as essential documents, section 8.1 of R2). In Annex 1 of R3, Appendix C redefines the concept of Essential Records and provides detailed operational guidance. The approach shifts from a static list of documents to be stored (as in E6(R2)) to a more flexible, principle-based view. It provides guidance on what constitutes an "essential" record, stating that the nature and extent of documents to be generated and maintained depend on the design and conduct of the trial, the application of proportionate risk approaches, and the importance and relevance of each record to the study's objectives. In other words, the essential nature of a document is linked to its contribution to participant safety or data validity: essential records are those that "enable the current management of the study and reconstruction of the trial" and document critical aspects such as compliance with the protocol, GCP, and regulations.

R3 clarifies the content, maintenance, and storage of these essential records. For example, it emphasizes maintaining the integrity and accessibility of these documents throughout their lifecycle (in line with data integrity requirements). The updated guidelines present a single table of examples of essential records (replacing the separate "before/during/after the study" lists in R2). This table includes, for example, essential documents such as the study protocol, the Investigator's Brochure (or basic product information if the drug is already marketed), approved informed consent forms, various approvals, and ethical opinions, etc. However, the focus is not so much on the list itself, but on the principle that each trial must identify its essential documents based on relevance and risk criteria. For smaller or simpler trials, fewer documents may be essential compared to large and complex trials, though certain elements (protocol, consents, and key data) remain fundamental in every case.

Another conceptual innovation is the reciprocity of access to essential documentation between sponsor and investigator. R3 clarifies that the sponsor and investigator/institution must have mutual access to each other's essential records, to the extent necessary to fulfil their responsibilities. This means, for example, that the sponsor should be able to access certain essential documents stored at the site (e.g., relevant source data, training certificates, etc.), and vice versa, the investigator should receive the sponsor's essential documents (e.g., product brochures, updated protocol, relevant SOPs, study reports, etc.). This approach promotes greater transparency and alignment between the study site and sponsor in managing the Trial Master File and Investigator Site File, ensuring that both parties have the necessary documentation to ensure the study's quality and compliance. Finally, R3 strengthens the guidelines on record retention: all essential data and documents (including electronic records) must be retained for the period required by regulations, accessible for inspections, with adequate integrity and protection controls (backup, IT security), and any planned destruction of records at the end of the retention period must be carried out according to documented procedures.

Digital Innovations and Decentralized Trials

The E6(R3) guidelines reflect the growing impact of digital technologies and new study models on clinical research, incorporating them into GCP principles. A crosscutting aspect of the document is its "media-neutral" approach, which is neutral to both paper and electronic media. This ensures that GCP requirements can be met whether traditional methods or advanced electronic systems are used in the trial, fostering technological innovation in clinical trials without losing sight of the basic principles. For example, R3 explicitly recognizes the use of digital health technologies (DHT), such as wearable devices, sensors, medical apps, etc., which can be integrated into trials to expand data collection and participant monitoring. These tools—possibly integrated into existing healthcare infrastructures—open new approaches for conducting studies, provided their use is appropriate for participant characteristics and trial design. The guidelines encourage sponsors to explore these digital innovations to make trials more efficient, for example, by facilitating patient recruitment and retention, collecting real-time data from diverse and complementary sources, and reducing site operational burden.

At the same time, R3 imposes stricter requirements for the governance of electronic data and cybersecurity. A new chapter dedicated to **Data Governance** highlights the importance of ensuring data integrity throughout its lifecycle, from initial collection to final analysis. Measures are required, such as appropriate validation of computerized systems used in the study (data collection software, eCRFs, clinical databases, eSource tools, etc.), controlled management of system accounts and access, the use of audit trails to track any changes to data, and adequate backup, security, and data protection plans to prevent unauthorized access or data loss. In practice, data integrity—that has been at the center of many regulatory inspections in recent years—is fully integrated into GCP: electronic data must be as reliable and verifiable as paper data. The guidelines urge sponsors and researchers to assess cybersecurity risks and implement proportionate measures to ensure the confidentiality of participant data and the availability of systems even in the event of failures or cyberattacks. This focus on electronic systems reflects the current reality, where much of the clinical data is managed digitally. It aims to ensure that technology is used responsibly without compromising patient rights or data quality.

A chapter of R3 is dedicated to decentralized trials and the use of "remote" study methods. Annex 1 redefines the concept of an investigator site more flexibly to include decentralized and virtual contexts. It is recognized that some study activities can take place outside traditional clinical sites, for example, at participants' homes or in peripheral healthcare facilities, without compromising GCP compliance. The guidelines provide guidance on how to manage such elements: for example, the sponsor must include in the monitoring plan and quality control strategies oversight of remote laboratories, pharmacies, or services involved in the study. Furthermore, R3 elevates the profile of centralized and remote monitoring: it is clarified that monitoring visits to sites can be conducted either on-site or remotely, and that a combination of centralized monitoring (e.g., remote analysis of accumulated data) and on-site monitoring can improve the effectiveness of controls. It is required that a study's monitoring strategy consider various factors (study objectives and phase, design complexity, blinding, product safety profile, etc.) and apply a risk-based approach to determine the frequency and intensity of visits, whether on-site or virtual. This codifies Risk-Based Monitoring into GCP, which was suggested in R2 but is now an integral part of the quality expectations in R3.

In general, R3 embraces innovative trial models. It is recognized that adaptive designs, decentralized or hybrid studies, pragmatic approaches, and the use of real-world data can bring benefits (e.g., greater inclusivity and more applicable results). At the same time, the guidelines provide a framework for implementing these innovations while maintaining ethical and quality standards. For example, the use of telemedicine tools, remote visits, or remote data collection must always occur with the participant's informed consent and under the researcher's oversight, ensuring the validity of remotely collected data as if it were collected on-site. Practical considerations are suggested, such as ensuring patients have the skills and resources to use any electronic devices provided by the study, planning technical support channels, and guaranteeing the protection of data transmitted to/from the patient. In essence, R3 normalizes decentralization as part of GCP, integrating it with principles of proportionality and a focus on quality: sponsors can leverage technologies and agile models to conduct studies, provided they assess and mitigate associated risks (e.g., device reliability, data security, training needs) and always keep participant protection and scientific data robustness at the center.

Patient-Centricity and Informed Consent

A crosscutting theme in R3 is the strengthening of patient orientation in the conduct of clinical trials. The revised guidelines explicitly promote patient inclusion and consideration of their viewpoints in various aspects of the process. It is stated, for example, that the use of innovative study designs and decentralized technologies can facilitate the participation of broader and more diverse patient populations, enhancing the representativeness and applicability of study results. Excluding specific participant categories without scientific justification should be discouraged: eligibility criteria should be scientifically justified to avoid unnecessarily limiting access to the study for subgroups (elderly, pregnant women, minorities, etc.) when not required by safety or scientific objectives. In line with the global focus on trial diversity, R3 pushes for more inclusive study designs to increase the results' generalizability and clinical impact.

Another significant change is the emphasis on active involvement of patients and other stakeholders (e.g., patient associations, caregivers, general practitioners) in the design and conduct of studies. Sponsors are encouraged to gather feedback from potential participants during the development of the protocol and informational materials to identify aspects that may be too burdensome or complex, potentially hindering study participation. Integrating the patient's perspective can help simplify unnecessarily complicated procedures, adopt more flexible visit schedules, reduce the burden

of redundant exams or questionnaires, and generally optimize the feasibility of the study while maintaining focus on important endpoints. This participatory approach aligns with the principles of patient centricity, now recognized as key factors for the success of modern clinical trials.

R3 also updates the Informed Consent process, adapting it to new practices and ethical expectations. Electronic consent (eConsent) and remote consent procedures are explicitly recognized and legitimized, provided that requirements for comprehensibility, voluntariness, and documentation are met. The guidelines encourage using technologies (tablets, video calls, and electronic signatures) to obtain consent when appropriate—for example, in fully decentralized trials—while ensuring the participant has the opportunity to ask questions and fully understand the study. In addition to the format, certain mandatory content of the information sheet and consent form has changed. R3 now requires the inclusion of information on the possible use of data and samples collected (e.g., biobanks, future research), explanations of how personal data will be protected, and a new mention of potential risks for third parties associated with the participant's involvement (e.g., risks to a sexual partner in the case of a teratogenic experimental treatment). Informed consent now also requires informing the participant about the existence of public study registries and offering the participant the possibility to be informed of the overall study results at the end (if desired). This marks a significant shift towards transparency and respect for study volunteers: participants are no longer seen simply as "subjects," but as partners in the study, deserving the right to know the outcome of the research to which they have contributed. In this sense, R3 prefers the term "participant."

R3 pays particular attention to vulnerable participants. Protections are strengthened for individuals who cannot give autonomous consent, for minors, and for groups potentially subject to coercion or exploitation. For example, the guidelines suggest additional safeguarding and ethical monitoring measures when involving vulnerable populations and reaffirm the need for consent from a legally acceptable representative when appropriate, along with the minor's assent when possible, in accordance with local regulations. Overall, the changes to the informed consent process aim to modernize and humanize it: leveraging technological tools and new information to make it more complete and convenient while ensuring the participant remains at the center, truly aware and respected in their rights and dignity.

Pros and cons

One of the main strengths of R3 is its flexible and proportionate approach. Unlike previous versions, it is no longer rigidly prescriptive, but encourages application proportionate to the risks for participants and the value of the data. This orientation should lead to a reduction of unnecessary bureaucratic burdens, allowing resources to be concentrated on critical quality aspects.

Linked to this aspect is the introduction of the quality by design concept. It is not only about conducting the study correctly but also about designing it from the outset with quality as an intrinsic objective, anticipating risks, and preventing errors that could compromise safety and data integrity.

Another positive novelty is the greater attention to data governance. Today, with growing digitalization and the use of real-world data, control over the entire data lifecycle—from collection to maintenance of blinding—becomes central. This also relates to the willingness to make the guidelines media-neutral, i.e., applicable regardless of paper or electronic format.

On the ethical level, R3 strengthens some fundamental aspects: informed consent is increasingly understood as a communication process rather than a simple signature, and greater commitment toward inclusivity is promoted in order to avoid unnecessary exclusions of categories of participants.

On the practical side, another clear strength is the opening to decentralized trials, the use of digital technologies, and the integration of real-world data. This represents a step forward to make clinical trials more agile and closer to the reality of medical practice.

Certainly, there are also critical issues. The first relates to the transition: adoption will not be uniform globally, and it is expected that some countries will move more quickly than others. For centers and sponsors, this means living, at least initially, with possible differences in interpretation and regulatory frameworks that are not fully harmonized.

A second limitation concerns costs and training commitments. The new structure, although clearer, introduces new concepts (e.g., data governance, delegated roles, and more detailed agreements), which will require significant investments in training, SOP updates, and contractual adjustments, as well as efforts in digitalization and validation of electronic systems that will not be easy to implement in clinical sites.

Finally, somewhat paradoxically, the very flexibility of R3 could become a double-edged sword: without equally detailed operational guidance, there is a risk of heterogeneity among sponsors, CROs, and regulatory authorities, with consequent differences in practical application.

In our view, these pros and cons should also be interpreted through the lens of the title of this article: evolution or revolution. Many of the changes—such as the risk-based approach, Quality Tolerance Limits, and clearer definitions of roles and responsibilities—are best considered evolutionary, representing a logical continuation and maturation of principles already anticipated in R2. These adjustments improve clarity and applicability but do not radically alter the framework of GCP.

By contrast, other provisions go well beyond incremental improvement and can be seen as revolutionary. The introduction of a modular architecture with annexes makes GCP a "living" guideline rather than a static one, fundamentally changing its nature. The explicit recognition of decentralized and hybrid trials, the integration of digital health technologies, and the central role of data governance and cybersecurity are disruptive elements that redefine what a clinical trial is and how it should be conducted. Perhaps most transformative is the emphasis on patient centricity: by re-framing the participant as a partner, encouraging inclusivity, and requiring return of results, R3 introduces a cultural shift as well as a technical one.

Therefore, the balance of pros and cons reflects this duality: R3 is evolutionary, where it consolidates and clarifies, but revolutionary, where it embraces new paradigms that will require significant adaptation by all stakeholders. This dual character is both a strength—allowing continuity with the past—and a challenge, as it demands readiness to embrace innovation while maintaining rigorous standards.

Table 1 lists the major differences between the R2 and R3 versions, as well as their impact.

TABLE 1 - Comparison between ICH E6(R2) and ICH E6(R3)

Area	R2	R3 (novelty)	Expected impact
Regulatory approach	Prescriptive guidelines, checklist-oriented	Flexible and proportionate, risk-based approach	↓ Administrative burden; ↑ Focus on critical aspects
Quality	Quality mainly, as compliance with processes and documents	Introduction of Quality by Design: quality embedded in study design	↑ Data robustness; ↓ Systematic errors
Data governance	Limited focus, mainly on source data verification and archiving	Dedicated section on data governance: data integrity, lifecycle, metadata, audit trail, blinding	↑ Data reliability; ↑ Digital compliance
Cybersecurity	Not specifically addressed	Explicit requirements for system validation, access control, audit trails, backup, and protection against cyber risks	↑ Data protection; ↑ System resilience
Document structure	Single text with sections on Sponsor and Investigator	Modular architecture: Principles, Annexes, Glossary, Appendices	↑ Clarity; ↑ Easier future updates
Ethics and consent	Strong focus on consent, mainly as a signed document	Consent as a communication process; emphasis on inclusivity and diversity	↑ Participant rights; ↑ Representativeness
Patient centricity	Participant seen as "subject" with a passive role	Participant as "partner"; inclusivity, return of results, engagement in design	↑ Transparency; ↑ Trust; ↑ Recruitment and retention
Study types	Focus on traditional interventional trials	Integration of decentralized trials, RWD, and digital tools	↑ Innovation; ↑ Access to trials
Monitoring and oversight	Predominantly on-site monitoring, document verification	Risk-based monitoring, integration of centralized and remote strategies	↑ Efficiency; ↓ Costs; ↑ Early detection of deviations
Roles and responsibilities	Delegations are possible, but with a limited focus on oversight	Clearer agreements, qualifications, and responsibilities (even if delegated)	↑ Accountability; ↑ Contractual complexity
Documentation	"Essential documents" are defined in a relatively static way	Updated appendices, media-neutral (paper/electronic)	↑ Flexibility; ↑ Use of digital systems
Global implementation	More uniform adoption, though gradual	Phased adoption, with possible regional differences	↑ Risk of initial heterogeneity
Training and quality culture	Focus on formal compliance	Emphasis on quality culture and continuous improvement	↑ Training investment; ↑ Sustainable improvement

Conclusion

Version R3 marks a new era for Good Clinical Practice, introducing concepts and flexibility that respond to transformations in recent years in the field of clinical trials. The key innovations—from the proportionate risk-based approach, quality by design, and better-defined roles to the embrace of digital technology, decentralized trials, and patient centricity—are all aimed at making clinical trials more efficient, ethical, and focused on truly critical aspects. For researchers, sponsors, clinical monitors, and all professionals in the clinical-regulatory field, the practical implementation of R3 will require an effort to update procedures, training, and mindsets. It will be crucial to adopt proactive quality systems, rethink monitoring and data management plans in a risk-based framework, engage patients early in study design, and ensure continuous technological compliance with GCP. The transition is already underway: version E6(R2) will

remain applicable until July 22, 2025, after which R3 provisions will become the new international standard. Ultimately, ICH E6(R3) strengthens the reliability and ethics of clinical research by introducing greater operational flexibility and a focus on quality. It is hoped that these changes will contribute to safer clinical trials for participants and more robust results, while fostering innovation and openness to modern experimental approaches.

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POINT OF VIEW

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PedEoEvolution: optimizing pediatric and adolescent eosinophilic esophagitis management in Italy

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ABSTRACT

This review addresses the unique challenges of pediatric eosinophilic esophagitis (EoE) management, aiming to develop a comprehensive knowledge base, standardize therapeutic approaches, and explore new targeted biological treatments. A non-systematic literature review was conducted, complemented by two surveys: one for clinicians to validate current practices and another for the President of the Italian Association of Families Against Eosinophilic Esophagitis to assess disease burden. An expert panel discussed and validated the results. The study identified a prevalence of 32.9 per 100,000 in pediatric EoE in Italy, with only half of the cases accurately diagnosed and an average diagnostic delay of 18 months. Current treatments show limitations in long-term management, with 27.8% of patients proving ineligible, intolerant, or inadequately controlled. The Impact Score and SCOPE (Symptoms, Comprehensive Observation, Pathological Evaluation) approach were recommended for early diagnosis and treatment efficacy evaluation. Dupilumab emerged as a promising therapy for patients unresponsive to conventional treatments, demonstrating significantly higher rates of histological remission in children aged 1-11 years compared to placebo in clinical trials. This study provides a standardized approach to pediatric EoE management, emphasizing early diagnosis, multidisciplinary care, and targeted biological treatments. The findings highlight the need for increased awareness, standardized care pathways, and further research to address ongoing challenges in pediatric EoE management.

Keywords: Disease management, Eosinophilic esophagitis, IMPACT score, Pediatric gastroenterology, Treatment algorithm

Introduction

Eosinophilic esophagitis (EoE) is a chronic, progressive, relapsing, type 2 inflammatory disorder of the esophagus, characterized by an abnormal accumulation of eosinophils in the esophageal epithelium (1,2). This condition, increasingly recognized in recent years, presents unique challenges in pediatric populations, where its management differs significantly from adult cases (3).

The etiology of EoE is multifactorial, involving a complex interplay of genetic predisposition, environmental factors, and immunological responses to antigenic stimuli (4). In young patients, the clinical presentation is often diverse and age-dependent, including symptoms such as dysphagia, food impaction, retrosternal pain, and manifestations mimicking gastroesophageal reflux (GERD). This broad spectrum of symptoms can make diagnosis challenging, particularly in younger children who may present with abdominal pain, vomiting, or failure to thrive (4-6).

EoE has gained increasing importance in the field of pediatric gastroenterology, necessitating greater awareness among healthcare professionals. Globally, the prevalence of EoE in the pediatric population is 32.9 cases per 100,000

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inhabitants, with an incidence rate of 4.9 cases per 100,000 person-years (7).

Diagnosis of EoE requires a comprehensive approach, integrating clinical history, endoscopic evaluation, and histological examination. The management of pediatric EoE necessitates a multidisciplinary strategy involving gastroenterologists, allergists, and pediatric specialists. Current therapeutic modalities include empiric food elimination diets, proton pump inhibitors (PPIs), topical corticosteroids (TCS), esophageal dilation in case of refractoriness (in the presence of strictures) and dupilumab, a monoclonal antibody targeting the shared receptor subunit of IL-4/IL-13, two interleukins central for type 2 inflammation. The latter is EMA-approved for patients aged 1 year and older with a body weight of at least 15 kg who are inadequately controlled by, intolerant to, or not candidates for conventional pharmacological therapy, and is currently reimbursed in Italy for adults and adolescents aged 12 years and older with a body weight of at least 40 kg meeting the same clinical criteria.

The management of EoE in children presents additional complexities related to long-term safety considerations, adherence challenges, and potential impacts on growth and development (5). These factors underscore the urgent need for standardized care pathways that ensure equitable access to appropriate treatments across different regions.

In light of these challenges and the evolving landscape of EoE management, there is a pressing need for comprehensive research to guide clinical practice in pediatric EoE. To address this need, our research aims to develop a comprehensive knowledge base on the management of pediatric patients with EoE. This research seeks to address existing knowledge gaps, standardize therapeutic approaches, and gather insights for positioning the new targeted biological treatment approved for EoE.

Our research aims to investigate the epidemiology of EoE in young patients (<12 years old) and to identify pediatric patients with EoE who are inadequately controlled by, intolerant to, or not candidates for conventional pharmacological therapy. These patients represent the target population for dupilumab treatment. Additionally, we examine patient management from diagnosis through treatment strategies to follow-up, identifying related gaps and critical issues. Importantly, we also explore the disease burden on patients' quality of life, recognizing the significant impact EoE has beyond its physical symptoms.

At last, this analysis aims to define an ideal therapeutic algorithm to standardize the treatment approach for pediatric and adolescent (up to 18 years old) EoE patients in Italy in order to contribute to more equitable and effective care for this patient population, addressing the unmet needs highlighted in the current landscape of EoE management.

Methods

A multi-faceted approach was employed to comprehensively assess the current landscape of EoE management in pediatric and adolescent patients. Initially, an in-depth literature review was conducted to map the patient journey and identify existing knowledge gaps. Based on these findings, two distinct questionnaires were developed: the first targeted clinicians to validate the literature review results, verify current clinical practices, and integrate additional aspects of EoE management. The second questionnaire, administered to the President of the Italian Association of Families Against Eosinophilic Esophagitis (ESEO Italia), was designed to gather the perspectives on EoE burden and quality of life from both patients and their families/caregivers. Subsequently, all interview results were shared and validated through a discussion panel composed of the same experts involved in the previous phases. This interdisciplinary approach facilitated a comprehensive overview of EoE management strategies, encompassing both clinical perspectives and patient experiences provided by the President of ESEO Italia, thus providing a more complete understanding of the challenges and needs in EoE care.

The research steps are illustrated in Table 1 and detailed below.

TABLE 1 – Research steps

Step	Activity	Detail
1	Expert Selection	An expert panel of 7 clinicians and the President of the patients association
2	Desk Research	A literature review was conducted to identify high-level information on EoE management.
3	Survey Drafting	The survey covered the topics of EoE management gaps and the patient journey.
4	Expert Interviews	The survey was administered to the expert panel through one-to-one sessions.
5	Results Analysis	Survey results were collected, analyzed and summarized.
6	Algorithm, Key Concepts and Final Meeting	An algorithm for disease management was developed, and key concepts were extrapolated and validated in a meeting.

Expert selection

For the purpose of evaluating the current management of EoE in the pediatric population and drawing key concepts to standardize patient care across the country, a panel of seven experts was selected. These experts were chosen based on their demonstrated experience in treating pediatric and adolescent patients with EoE. The selection process ensured that the affiliated institutions of the involved experts provided a representative geographical distribution across the national territory (Fig. 1). To incorporate a comprehensive perspective on the disease burden, the President of the patient association ESEO Italia was also included in the panel.

Desk research

A non-systematic literature review was conducted by the authors, following shared research objectives, with the purpose of constructing an essential knowledge framework concerning the epidemiology of the pediatric population, as well as the diagnostic and therapeutic strategies for pediatric/adolescent patients with EoE. The results were subsequently presented to the expert panel for validation and integration with real-world clinical insights.

FIGURE 1 - Key red flags and best practices in clinical, endoscopic, and histologic assessment.
Acronyms: DSQ: Dysphagia Symptom Questionnaire; EoE: Eosinophilic Esophagitis; eos/hpf: Eosinophils per High-Power Field; eos/hpf: Eosinophils per High-Power Field; GERD: Gastroesophageal Reflux; PEESS: Pediatric Eosinophilic Esophagitis Symptom Severity; PESQ: Pediatric Eosinophilic Esophagitis Sign/Symptom Questionnaire; PPI: Proton Pump Inhibitors; TCS: Topical Corticosteroids.

Survey drafting

Following the desk research, two distinct surveys were developed to address specific aspects of EoE management. The first survey, directed at clinicians, comprised 28 questions divided into six main themes: (i) epidemiology, (ii) diagnostic pathway, (iii) therapeutic approaches, (iv) follow-up, (v) unmet needs, (vi) potential role of new targeted biological therapies in the condition under consideration (Supplementary Material 1). This survey aimed to bridge gaps in understanding the patient's diagnostic and therapeutic pathway, verify the most prevalent therapeutic approaches, and validate the epidemiological funnel.

The second survey, designed for the President of ESEO Italia, consisted of 33 questions (Supplementary Material 2). These were categorized into four areas: (i) daily management and quality of life, (ii) diagnosis and symptomatology, (iii) costs and services, (iv) therapeutic needs.

The primary objectives of this survey were to delineate the disease burden and assess the impact of EoE on patients and their families or caregivers.

Both surveys were constructed based on the findings from the literature review, ensuring that they addressed key areas of interest and potential knowledge gaps identified in the literature review.

Expert interviews

The surveys were administered to the involved experts through private, web-based, one-on-one sessions in an interview format. This approach allowed for a more dynamic and interactive data collection process, enabling the experts to provide in-depth responses and additional comments beyond the structured questions. The one-on-one nature of these sessions ensured confidentiality and allowed each expert to express their views freely without influence from peers. This methodology maximized the quality and depth of the

information gathered, providing a rich dataset for subsequent analysis and consensus-building efforts in standardizing EoE management across the national context.

Results analysis

Following the interviews, results were collated and compared through a qualitative analysis, highlighting areas of consensus and divergence among experts. Points of agreement formed the basis for preliminary recommendations, while areas of disagreement were identified for further discussion. This process ensured that the final outputs would reflect both established practices and address current uncertainties in EoE management.

Algorithm, key concepts drafting and final meeting

The analysis of results allowed the validation of the patient funnel, identifying the burden of pediatric patients (under 12 years old) with EoE who are inadequately controlled, intolerant, or ineligible for current treatments. Additionally, key messages were formulated regarding patient management throughout the diagnostic, therapeutic, and follow-up pathway, and a management algorithm was developed synthesizing the key steps of the care process. These elements were subsequently shared and further validated in the context of a final meeting involving all the experts interviewed in the previous phases of the project. Although the experts who participated in the final discussion also completed the initial questionnaires, their individual responses were collected independently and anonymously prior to the meeting. The final discussion aimed to synthesize collective insights and address areas of divergence, rather than to retrospectively validate or modify individual answers. During this session, the proposed key messages were discussed, and participants expressed their agreement with the aim of standardizing the approach to care and management of pediatric and adolescent patients with EoE.

Results

This section presents aggregated results that integrate findings from the literature review with clinical practice insights gathered through surveys and discussed collectively during a dedicated expert meeting.

Epidemiology

The first objective of the survey was to identify pediatric patients with EoE who are ineligible, intolerant, or inadequately controlled by current treatments.

The analysis started from pediatric EoE global prevalence reported by Hahn et al. (2023) of 32.9 patients per 100,000 and a European rate of 20.5 per 100,000 (7). Despite the lower European average, experts suggest that in the national context, particularly in Italy, the prevalence is more likely to align with the global rate of 32.9 per 100,000, similar to the situation observed in Spain (7).

The survey explored the percentage of patients correctly diagnosed, given that EoE presents similar symptoms and can often be confused with related conditions (such as GERD and dyspepsia) (8). On average, experts estimate that only 50% of prevalent cases receive an accurate diagnosis. However, once diagnosed, 100% of patients receive treatment, either pharmacological or dietary. Among these treated patients, literature evidence indicates that between 27.3% and 30.3% prove to be ineligible, intolerant, or inadequately controlled by currently available treatments, despite proper management (9). Finally, considering the population under 12 years old residing in Italy as of January 1, 2024 (10), it is estimated that approximately 260 patients with EoE are ineligible, intolerant, or inadequately controlled by current treatments (Table 2). This number identifies patients potentially eligible for treatment with a new biological drug (once authorized).

TABLE 2 - Epidemiology of pediatric EoE patients

People resident in Italy as of 1 January 2024 (<12 years)		**5,498,128 (10)**
Patients with EoE (prevalence)	32.9 per 100,000 (0.0329%) (7)	**1,809**
Correctly diagnosed patients	50%*	**904**
Patients diagnosed with EoE receiving treatment	100%*	**904**
Ineligible, intolerant, inadequately controlled patients	28.8% (9)	**260**

*Experts' opinion

Algorithm and key concepts for disease management

Diagnostic pathway and challenges in pediatric/adolescent EoE

The experts report a notable difference in diagnostic delay between pediatric/adolescent and adult populations with EoE. For the pediatric and adolescent group, the average diagnostic delay is approximately 18 months, substantially lower than the 3-year delay observed in adults (8). This reduced delay is attributed to heightened attention to pediatric and adolescent health concerns. Moreover, according to the experts, the presence of comorbidities may further shorten this delay.

Based on survey results, the experts identified several factors that contribute to the diagnostic delay:

- Adaptive behaviors: Patients often develop instinctive adaptive behaviors that mask the disorder, potentially delaying suspicion of EoE until symptoms reach a critical point.
- Limited disease awareness: There is a general lack of widespread, comprehensive knowledge about EoE among healthcare providers.
- Challenging sophisticated differential diagnosis: EoE is frequently misdiagnosed as other diseases, particularly GERD.

Concerning adaptive behaviors, to facilitate early diagnosis and assess treatment efficacy in EoE, experts suggest the implementation of the **IMPACT Score**. This tool consists of 10 targeted questions designed to uncover adaptive behaviors that may obscure the underlying condition (Table 3) (11-13).

TABLE 3 - Impact Score (11,12)

I	M	P	A	C	T
Imbibe fluids with meals	Modify food	Prolong mealtime	Avoid textured food	Chew excessively	Turn away tablets/ pills

10 possible questions to ask the patient to identify adaptive behaviors masking the manifestation of EoE symptoms

Question	YES	NO	Assign a score from 1 to 10 to express frequency or intensity
1. Do you get food stuck while swallowing it?	□	□	
2. Do you feel you have to chew more or longer to swallow your food without difficulty?	□	□	
3. Does it take you longer than others to finish your meal?	□	□	
4. Are you typically the last one to finish eating?	□	□	
5. Do you need to cut food into small pieces?	□	□	
6. Do you need to soften certain foods that you find harder?	□	□	
7. Do you drink a lot of water during meals to facilitate swallowing?	□	□	
8. Do you often avoid going out to eat?	□	□	
9. Have you ever had to resort to excuses to avoid eating in public?	□	□	
10. Are there any foods you avoid? If yes, please indicate which ones.	□	□	

The IMPACT Score's application extends beyond patients with overt eating-related symptoms. Experts advocate its use in patients presenting with other immune-inflammatory conditions such as asthma, rhinitis, and food allergies, as these individuals may harbor subclinical EoE symptoms.

Each question in the IMPACT Score is rated on a scale of 1-10. This approach facilitates accurate diagnosis by revealing the subtle impacts of EoE that might otherwise go unnoticed.

The IMPACT score thus emerges as a valuable asset in the diagnostic toolkit for EoE, offering a structured method to quantify and interpret the subtle behavioral adaptations characteristic of this condition.

Furthermore, to address these challenges and improve diagnostic accuracy and timeliness, the involved experts formulated a set of suggestions, as illustrated in Figure 2. This figure outlines the 'red flags' to be vigilant for at clinical, endoscopic, and histological evaluation levels, along with corresponding best practice guidelines for effective and prompt diagnosis.

This strategy highlights the critical need for a comprehensive diagnostic assessment in EoE, integrating clinical evaluations, endoscopic investigations, and histopathological studies to guarantee a thorough and prompt diagnosis in young patients. Given that EoE is a chronic, progressive, and type 2 immune-mediated inflammatory disease, experts emphasize the critical importance of considering the potential coexistence of other type 2 inflammation-mediated conditions. This consideration is crucial for a holistic understanding of the patient's health status and for tailoring appropriate treatment strategies.

Finally, to guarantee an accurate and complete evaluation, a multidisciplinary approach is strongly recommended. This approach should involve key specialists, including a gastroenterologist, allergist, pathologist and possibly a psychologist. This collaborative, multidisciplinary strategy ensures that all aspects of the patient's condition are thoroughly examined and addressed, leading to more effective diagnosis, management, and long-term care of pediatric and adolescent EoE patients.

Current therapeutic approaches and follow-up

The therapeutic approach for EoE encompasses a range of options, including pharmacological interventions, dietary modifications, and esophageal dilation. Budesonide orodispersible tablets have been approved for marketing and granted reimbursement for the treatment of adult patients in most European countries (Italy included), and dupilumab is approved by both FDA and EMA for patients aged 12 and above and by FDA for patients aged ≥1 year and weighting ≥15 kg (6), and it has been reimbursed in Italy for patients ≥12 years weighting ≥40 kg. However, it is crucial to note that, as of now, there are no treatments specifically approved for the pediatric population in Italy below 12 years of age at the time of this manuscript's drafting. Consequently, in pediatric practice, experts rely on the off-label use of PPIs and TCSs, whereas dupilumab is the newly approved treatment in the adolescent age (12-17 years) in Italy.

The therapeutic choice should be thoroughly discussed with the patient and their family or caregivers (6). This collaborative approach ensures that all parties are informed about the off-label nature of the treatments currently employed in pediatric EoE management and can make informed decisions about the care plan.

FIGURE 2 - Treatment and follow-up management algorithm of paediatric/adolescent EoE patients.
*The evaluation shall be conducted using S.C.O.P.E. (Symptoms, Comprehensive Observation, Pathological Evaluation), i.e., the all-comprehensive approach that takes into account symptoms (severity, frequency, etc.), comprehensive observation (adaptive behaviour, concern about diet/weight, etc.) and pathological assessment (endoscopy findings, biopsy, etc).
The red circle with the warning triangle highlights points of attention in the pathway.
The green rectangle with a dashed border indicates therapeutic approaches that may be implemented alongside the pharmacological approach.
Acronyms: **DSQ:** Dysphagia Symptom Questionnaire; **EoE:** Eosinophilic Esophagitis; **eos/hpf:** Eosinophils per High-Power Field; **EREFS:** Endoscopic Reference Score; **HSS:** Histology Scoring System; **PEESS:** Pediatric Eosinophilic Esophagitis Symptom Severity; **PESQ-C:** Pediatric Eosinophilic Esophagitis Sign/Symptom Questionnaire – Caregiver; **Type 2i:** Type 2 Immune-mediated inflammatory disease.

Treatment typically begins with conventional off-label therapies such as PPI (especially when GERD is present) and TCS. The primary objectives of EoE treatment are to control symptoms, reduce esophageal inflammation, and prevent complications (6, 11). In cases of severe esophageal narrowing, dilation may be strongly suggested (6). Although elimination diets offer a non-pharmacological alternative, adherence can be challenging due to their restrictive nature.

The efficacy of the induction therapy is evaluated 8-12 weeks after initiation (5). If remission is achieved, the same treatment is continued long-term. However, if the patient is not adequately controlled, it is crucial to verify treatment adherence and consider switching to biological therapy, once available.

For patients on biological therapy, efficacy is assessed after 12-16 weeks. If the disease is in remission, long-term treatment is maintained. Long-term management is crucial even if clinical symptoms are absent (14): the experts involved recommend an endoscopy within 9 months of the initial evaluation and, after the first year, in the absence of symptoms, alternating clinical and endoscopic evaluations (with biopsy) are recommended at 6-month or 1-year intervals.

In the evaluation of treatment efficacy, experts emphasize the importance of a multidimensional assessment that simultaneously considers clinical, histological, and endoscopic evaluations. They further stress that this comprehensive approach is crucial to reveal hidden progression and uncover patients who are not fully controlled, ensuring a more accurate assessment of the disease state.

To support this multidimensional evaluation, the SCOPE (Symptoms, Comprehensive Observation, Pathological Evaluation) approach has been recommended. SCOPE is an all-encompassing method that guides the assessment of symptoms (evaluating severity and frequency), comprehensive observation of adaptive behaviors (using the IMPACT Score), diet/weight-related issues, and completed therapy cycles, and pathological evaluation through endoscopy with biopsy, detecting visible changes in the esophagus, calculating EREFS (Endoscopic Reference Score), eosinophil count and HSS (Histology Scoring System) Score.

This holistic SCOPE approach aids in determining whether there is a response to therapy and if a treatment switch is necessary. By integrating symptomatic, adaptive-behavioral (assessed by IMPACT), and pathological (assessed by

endoscopic and histologic scores and eosinophil count) aspects, SCOPE provides a more nuanced and accurate picture of the patient's condition and treatment progress.

This structured follow-up protocol ensures continuous monitoring of disease activity and treatment efficacy, allowing for timely adjustments in the therapeutic approach and maintaining optimal control of EoE in pediatric and adolescent patients.

Finally, regardless of the pharmacological choice, the chronic and progressive nature of EoE requires ongoing continuous treatment. Indeed, failure to maintain prolonged symptom control increases the likelihood of recurrence, and patients who do not have continuous and sustained histological control are at increased risk of developing fibrosis (15). Some clinicians report using cyclic therapy to reduce the risk of long-term side effects. This is due to concerns about the safety of prolonged treatment and poor compliance.

However, as mentioned above, literature data show greater efficacy with continuous therapy (16).

Limitations of current therapies and the potential role of new biological anti-IL-4 and IL-13 drugs in pediatric and adolescent EoE

The management of EoE in pediatric and adolescent patients presents significant challenges due to the limitations of currently available therapies.

While TCS are effective in inducing EoE remission and can provide clinical and histological improvement, their long-term use is associated with substantial side effects (6), making them unsuitable for chronic management of EoE. To date, no TCS has been approved for children. However, for adults over 18 years old, the EMA has approved an effervescent tablet that releases budesonide in the oral cavity to be swallowed with saliva. This has shown efficacy both in inducing remission (58% at Week 6 and 87% at Week 12) and in maintenance, with a range of 73.5–75% at Week 48 (17-19), which has been confirmed by recently published long-term follow-up data (20). Recently, the FDA approved a budesonide oral suspension for the induction treatment of patients with EoE over 11 years old. Currently, the use of oral topical steroids in children younger than this age, or where the drug is not commercially available (17-19), remains off-label, although several clinical trials of new formulations for children are underway. Experts (5) report that the primary adverse events associated with long-term steroid use include alterations in the glycemic curve, suppression of the hypothalamic-pituitary-adrenal axis, and the occurrence of recurrent candidiasis. These side effects often lead to treatment discontinuation, defining a subset of patients as intolerant to TCS therapy. Additionally, patients with recurrent infections or immunosuppression are not candidates for TCS treatment, further limiting its applicability.

PPI treatment can achieve clinical and histological remission in a significant proportion of patients with EoE. However, this approach is currently off-label, and long-term maintenance data have a low level of evidence. Moreover, during extended follow-up, potential adverse effects should be considered, including an increased risk of fractures, intestinal dysbiosis, and deficiencies in certain micronutrients, although these are rare (6).

Beyond the patients who are ineligible for or intolerant to these treatments, there is a significant proportion of patients who are inadequately controlled by current therapies. These are patients who, despite adherence to prescribed treatment, continue to experience persistent or recurrent symptoms typical of active disease. This situation highlights a substantial unmet need in the pediatric and adolescent EoE population, where patients have limited therapeutic alternatives. In this context, experts suggest that a targeted biological treatment like dupilumab represents a new therapeutic approach in the management of pediatric and adolescent EoE. This drug, by targeting the underlying pathophysiology of EoE, has the potential to address this unmet need and may slow the progressive evolution of the disease, potentially transforming its course. This potential has been demonstrated in the phase 3 EoE KIDS study, showing significantly higher rates of histological remission in children aged 1-11 years compared to the placebo arm (21), as well as in the TREET study, in which adolescents have been included (22).

The introduction of an anti-IL4 and IL-13 biological treatment for pediatric and adolescent EoE patients who are unresponsive to, intolerant to, or ineligible for conventional therapies could represent a significant advancement in care. Its mechanism of action, targeting the root cause of the disease (i.e., IL-4 and IL-13, which are key and central drivers of type 2 inflammation), offers the possibility of not just managing symptoms, but potentially altering the disease trajectory. Safety profile during studies in EoE was consistent with the known dupilumab safety profile (23). Additionally, transcriptomic data from clinical studies have shown the potential for improving the signature associated with type 2 inflammation and the EoE Diagnostic Panel (EDP) (21). The experts agree that this treatment could offer an alternative for patients who are ineligible for, intolerant to, or inadequately controlled on current therapies, but also for patients who have rapidly progressing and aggressive disease with an increased tendency to develop fibrostenosis since confirmation of diagnosis.

The impact of pediatric/adolescent EoE on patients and families/carers

A comprehensive discussion with the President of ESEO Italia and the expert panel has revealed the profound impact of EoE on pediatric/adolescent patients and their families. The disease significantly affects daily life, with meal preparation and consumption becoming central to family routines. This constant focus on food and eating habits not only disrupts normal daily activities but also places a considerable psychological burden on both patients and caregivers.

EoE's influence extends beyond the physical aspects of food consumption, significantly impacting social relationships. Patients, especially children and adolescents, may experience challenges in personality development and self-esteem, leading to substantial psychological repercussions. The disease necessitates a consistently high level of vigilance from patients and families in organizing meals, administering medications, and anticipating potential challenges in everyday situations.

To address these challenges, the experts emphasized the critical need for increased awareness and education about EoE. Promoting knowledge about the disease and its early warning signs among healthcare providers and the general

public is crucial for facilitating early diagnosis. Timely identification and intervention can lead to more favorable prognoses and improved quality of life for patients.

Another key point raised was the necessity of standardizing care pathways and access to services across the country, especially during the transition of patients from pediatric to adult care, to avoid loss to follow-up and waste of healthcare resources due to disease progression and complications. Creating transitional care centers of excellence ensures continuous management for all patients, regardless of their geographical location, and is fundamental in providing consistent and high-quality care for EoE patients nationwide.

This insight into the lived experience of EoE patients and their families underscores the complex nature of the disease's impact and highlights the areas where improvements in care and support systems could significantly enhance patient outcomes and quality of life.

Discussion

This study provides a comprehensive overview of the current landscape of pediatric EoE management in Italy, highlighting several critical areas for improvement and future research.

One of the key issues identified is the significant diagnostic delay in pediatric EoE, averaging 18 months. Although the diagnostic delay is even longer in the adult population, this delay remains one of the major critical issues in pediatric/adolescent patients as well, impacting timely intervention and disease management. This delay is largely due to the diverse and often nonspecific symptoms that mimic other conditions, such as GERD. The implementation of the IMPACT Score as a diagnostic tool could potentially reduce this delay by uncovering adaptive behaviors that mask the disease, allowing for earlier and more accurate diagnosis.

The analysis also underscores the limitations of current treatments, including PPIs and TCS, which are often used off-label in pediatric patients. The lack of approved therapies for children under 12 years old in Italy highlights a significant unmet need. The emergence of a targeted biological therapy offers a potential alternative, particularly for patients unresponsive to conventional treatments.

A notable contribution of this study is the proposed SCOPE approach for evaluating treatment efficacy. By integrating clinical, histological, and endoscopic assessments, this multidimensional evaluation provides a more comprehensive understanding of the disease state and treatment response. This approach is crucial for identifying patients who are not fully controlled and for making timely adjustments to their treatment plans.

The importance of a multidisciplinary approach is also emphasized. Involving gastroenterologists, allergists, pathologists, and psychologists ensures that all aspects of the patient's condition are addressed, from diagnosis to long-term management. This collaborative strategy supports the holistic care of pediatric EoE patients, improving overall outcomes.

The analysis highlights the need for standardized transitional care pathways to ensure continuous and consistent management of EoE as patients move from pediatric to adult care. This approach is essential to prevent loss to follow-up and to maintain the quality of care throughout the patient's life.

Additionally, the discussion addresses the significant impact of EoE on the quality of life of patients and their families: the constant attention required regarding food choices and eating habits, along with the psychological burden associated with the disease, underscores the need for increased awareness and education about the disease. Promoting knowledge among healthcare providers and the general

TABLE 4 - Summary of key concepts emerging from survey and discussion

1	Implement the IMPACT Score to uncover adaptive behaviors and facilitate early EoE diagnosis, especially in patients with other immune-inflammatory conditions.
2	As EoE is a chronic, progressive, type 2 immuno-inflammatory pathology: in the diagnostic process, for a correct diagnosis, it is essential to consider the possible coexistence of other pathologies mediated by type 2 inflammation (such as atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyps, allergic rhinitis, chronic spontaneous urticaria); a multidisciplinary evaluation by a gastroenterologist, an allergist and an anatomopathologist, with possible psychological support, is considered best practice. This integrated approach allows a more complete and accurate assessment of the patient.
3	In the treatment of EoE in paediatric/adolescent patients, the presence of comorbidities, type 2 inflammatory diseases, disease-associated growth problems, recurrent candidiasis/infections or immunodepressed states directs the therapeutic approach towards the use of biological drugs.
4	In order to assess therapeutic efficacy and verify disease remission, it is essential to perform a multidimensional assessment that simultaneously considers clinical, histological and endoscopic evaluations. Such an integrated approach, supported by the comprehensive SCOPE approach, provides an accurate understanding of the patient's health status and the effectiveness of the therapeutic treatment.
5	Patients with EoE require chronic continuous, rather than intermittent (cycling/stacking) therapy to achieve continuous and prolonged control of symptoms and histology and endoscopic aspects, and to prevent the development of fibrostenotic complications in the long term.
6	It is necessary to promote education about the disease and the warning signs that should raise suspicion, such as the IMPACT score, to be used in open day initiatives and public awareness campaigns, in order to achieve early diagnosis and ensure a more favorable prognosis with a better quality of life.
7	It is necessary to create standardized Transitional Care Pathways to ensure continuous and consistent treatment for patients with EoE as they transition from pediatric to adult care (6). This approach aligns with best practices and helps maintain the quality of care throughout a patient's life.

public can facilitate early diagnosis and improve patient outcomes.

Limitations of the Study

The non-systematic nature of the literature review may have led to the omission of relevant studies. The reliance on expert opinion and surveys introduces potential biases, as the findings are based on the perspectives of a limited number of specialists. Additionally, the study's focus on the Italian context may limit the generalizability of the results to other regions with different healthcare systems and patient populations. Future research should aim to include a broader range of data sources and consider longitudinal studies to validate the proposed diagnostic and therapeutic approaches.

Moreover, we acknowledge that the experts involved in the final consensus meeting were the same individuals who participated in the survey phase. While this may introduce a risk of bias, the design of the process—particularly the use of independent, one-to-one interviews—was intended to mitigate this limitation. Future studies may consider incorporating external validation panels or Delphi rounds to strengthen methodological robustness.

Conclusion

This comprehensive analysis of pediatric and adolescent EoE management has yielded valuable insights for standardizing care across Italy. The proposed diagnostic and therapeutic algorithms, along with the emphasis on multidisciplinary care, provide a solid foundation for improving patient outcomes. However, several areas require further attention and development such as the creation of a shared pathway for transitional age patients to ensure continuity during the passage from pediatric to adult care and address the unique challenges of this period; the establishment of a national disease registry which would facilitate research, improve understanding of disease patterns, and enhance patient care; the promotion of multidisciplinary care to ensure its widespread implementation across healthcare settings and the standardization of care pathways across different regions of Italy.

Addressing these open points will be crucial in further advancing the management of pediatric and adolescent EoE and improving the quality of life for affected patients and their families.

Disclosures

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POINT OF VIEW

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From data to evidence: the evolving role of observational studies and target trial emulation in regulatory decision-making

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ABSTRACT

Introduction: The European Medicines Agency (EMA) has updated its Reflection Paper on the use of Real-World Data (RWD) in Observational Studies (OS), emphasizing the regulatory importance of Real-World Evidence (RWE).
Objectives: Summarize the main methodological recommendations of the EMA's 2025 guidance, highlight challenges and opportunities for the use of RWD in regulatory contexts, and discuss implications for clinical researchers, with particular attention to the role of pharmacists.
Discussion: The new guidance distinguishes descriptive from causal OS and endorses Target Trial Emulation (TTE) to improve causal inference in observational research. It stresses transparency, reproducibility, and rigorous data governance, while calling for robust strategies to manage bias and confounding. Pharmacists are recognized as key contributors to drug utilization research and post-marketing surveillance, ensuring data quality and interoperability and supporting the integration of RWE into regulatory decision-making.
Conclusions: EMA's roadmap affirms the value of RWE in strengthening regulatory science. Its implementation will require cultural change, technical expertise, and resource allocation, offering both challenges and opportunities for healthcare researchers, particularly pharmacists, to transform RWD into trusted evidence.

Keywords: Clinical pharmacy, Drug utilization, Observational studies, Real-world evidence, Target trial emulation

Introduction

In recent years, Real-World Evidence (RWE) has gained significant traction as a complementary source of information to traditional randomized controlled trials (RCTs) in the evaluation of medical interventions. The European Medicines Agency (EMA), through its updated 2025 Reflection Paper, offers a detailed regulatory perspective on how Real-World Data (RWD) should be leveraged in Non-Interventional Studies (NIS) to inform healthcare decision-making. In line with regulatory frameworks, RWE can also be generated from randomized designs such as pragmatic or large simple trials when conducted under real-world conditions. This article aims to explore the conceptual and methodological shifts introduced by the EMA and highlight their implications for clinical researchers, with a focus on the evolving role of pharmacists.

The Regulatory Weight of Observational Evidence

RCTs remain the gold standard for demonstrating efficacy and safety. However, their rigid structure and exclusion criteria limit their external validity. In contrast, OS allow for the observation of treatment effects in real-world settings, capturing clinical complexity, comorbidities, and variations in adherence. Recognizing this, EMA now provides clearer recommendations for when and how RWD can be used to generate RWE for regulatory purposes (1).

Accordingly, EMA underscores the importance of adhering to established methodological standards - such as those provided in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)

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Guide (2)—and of using structured tools, like checklists and visual design aids, to enhance the rigor, clarity, and transparency of observational studies (OS).

Descriptive vs. Causal OS*: a Conceptual Framework*

The updated Reflection Paper draws a critical distinction between descriptive and causal OS. Descriptive studies focus on patterns of drug utilization, prevalence, incidence, and user characteristics. Causal OS, on the other hand, aims to infer treatment effects. Descriptive studies also demand rigorous upfront work: transparent a priori outcome definitions; validation of coding algorithms; assessment of data quality (completeness, timeliness, accuracy); and explicit sampling rules to prevent selection artifacts. Importantly, neither observational nor randomized studies necessarily mirror routine practice: external validity depends on protocol choices (e.g., inclusion/exclusion criteria, follow-up intensity, outcome definitions) and on the study's position along the 'pragmatism' continuum.

Target Trial *Emulation: A Methodological Evolution*

Among the most significant contributions of the new EMA guidance is the endorsement of Target Trial Emulation (TTE) as a methodological standard for causal inference in OS (3).

Traditional OS, while essential, have often been limited in their ability to infer causal relationships.

Target Trial Emulation (TTE) tackles the inherent limitations of OS by first imagining the RCT that would provide the best possible answer to the research question, if conducting it were feasible. This "target trial" is defined in detail as eligibility criteria, treatment strategies, assignment procedures, follow-up, and outcomes, and then these elements are systematically reproduced using RWD. In doing so, TTE may allow researchers to bring the methodological rigor of RCTs into observational settings, narrowing the gap between the practical constraints of RWD and the reliability of evidence generated by randomized trials. This approach aligns the definition of time zero for eligibility, treatment assignment, and follow-up, to avoid immortal time bias and other common pitfalls. Statistical methods may be used to adjust for baseline differences, approximating the balance achieved through randomization. Consequently, TTE enhances causal inference from RWD, improving the validity and applicability of findings on drug effectiveness and safety in routine clinical practice. TTE may offer a powerful framework to generate timely, robust evidence, supporting more informed decisions by clinicians, regulators and payers, particularly in contexts where RCTs are unethical, impractical, or prohibitively expensive. Alongside observational approaches, pragmatic randomized trials remain an important pathway to generate RWE.

Managing Bias and Confounding in OS

Because of their observational design, OS are inherently exposed to biases that may threaten the validity of their findings. Selection processes, misclassification of exposures or outcomes, and uncontrolled confounding can all distort the estimated associations and hinder causal interpretation. To mitigate these risks, careful study planning, appropriate analytical strategies, and transparent reporting are required. In addition, attention must be paid to potential effect modification to identify population characteristics that shape treatment outcomes and determine the extent to which results can be generalized to the intended target population.

Also, within the TTE framework, rigorous control of bias and confounding is essential to preserve internal validity. While the approach is designed to reduce distortions common in OS, it remains susceptible to systematic errors, particularly those arising from incorrect specification of time zero, exposure misclassification, and residual confounding.

Immortal time bias can be minimized by clearly defining the eligibility window and ensuring precise temporal alignment between cohort entry and exposure assignment. To address confounding, investigators should pre-specify a set of baseline covariates measured prior to exposure initiation, ideally informed by a Directed Acyclic Graph (DAG) representing the hypothesized causal structure.

Recommended strategies include:

i) Restriction and matching on key covariates to enhance comparability across exposure groups.
ii) Inverse probability of treatment weighting (IPTW) based on propensity score models to balance baseline characteristics.
iii) Multivariable outcome modeling to further adjust for residual confounding.
iv) Doubly robust estimators, combining treatment and outcome models, to reduce susceptibility to model misspecification.

Sensitivity analyses, such as the E-value or quantitative bias analysis (4,5), should be used to evaluate the potential impact of unmeasured confounding and to test robustness under alternative definitions of exposure and outcome.

Transparent reporting of all methodological decisions, including underlying assumptions and exclusion criteria, is essential to facilitate replication and critical appraisal.

Operationalizing RWE: Data Quality and Transparency

Generating credible RWE depends on the quality and traceability of the underlying RWD. The EMA highlights the importance of robust data governance, including pre-specification of outcomes and minimum quality thresholds for analytic datasets, ensuring that information is collected and processed in compliance with data protection regulations and ethical standards. It also calls for prospective study registration and the availability of raw datasets to guarantee reproducibility. Equally crucial is transparency, with full disclosure of protocols, analysis plans, and sensitivity analyses in line with the principles of ICH E6(R3) and E9(R1) (6,7). These requirements, though demanding, elevate the scientific credibility of OS and reinforce the accountability of researchers.

Linkage and Completeness: The Italian Challenge

In Italy, the regionalized structure of the NHS presents a unique and persistent challenge to the integration of RWD. Despite several attempts at harmonization, the lack of a national interoperable data infrastructure and the absence of common standards for data storage and exchange continue to hinder access to complete and unified datasets (8). Electronic

health records, administrative claims, disease registries, and pharmacy dispensing data are often 'siloed' within individual regions or institutions, making linkage difficult and analysis fragmentary.

This fragmented landscape not only limits the generalizability of OS but also undermines the reliability of RWE for national regulatory or HTA decision-making. While some regions have developed advanced local data systems, e.g., "Edotto" system in Apulia, the national picture remains heterogeneous, and no central repository or federated model has yet been fully implemented. The resulting lack of interoperability and the variable quality of data across territories prevent a consistent, country-wide approach to evidence generation.

A partial but promising response to these challenges is represented by the ongoing development of the Electronic Health Record (EHR), or Fascicolo Sanitario Elettronico (FSE). Initially introduced by Legislative Decree No. 179/2012 (9) and strengthened by subsequent reforms [notably Budget Law 2020 and the Ministerial Decree of May 20, 2022 (10)], the FSE is intended to be a unified digital platform for collecting, storing, and sharing patient data across all Italian regions. Its full implementation, now backed by investments from the National Recovery and Resilience Plan (PNRR - Mission 6) (11), aims to ensure nationwide interoperability and accessibility to healthcare data for both care and research purposes.

However, progress has been uneven. As of 2024, many regions have not yet achieved full compliance with the FSE integration standards, and concerns remain about governance, data quality, and patient privacy. The success of the FSE will depend on effective coordination among national and regional authorities, robust IT infrastructure, and active engagement from healthcare professionals (12).

In line with the PNRR milestones, FSE 2.0 is expected to reach: (i) ≥85% of general practitioners feeding the FSE by Q4-2025 (M6C2-11); (ii) full operation of the Electronic Health Card system and the national FSE interoperability infrastructure by mid-2026 (T2-2026; M6C2-12); and (iii) nationwide adoption and use across all 21 Regions/Autonomous Provinces by mid-2026 (T2-2026; M6C2-13). Progressive targets also include stepped increases in GP participation (≈5% mid-2023; ≈30% mid-2024; 85% H2-2025) and document indexation towards ≈90% by mid-2026 (13). In this context, pharmacists and local health professionals are often the only actors with continuous access to patient-level data in real time, and their engagement in data capture and validation becomes even more critical. They can serve as data stewards, ensuring that what is collected at the point of care can be leveraged for high-quality RWE studies with national relevance.

Pharmacists at the Forefront: From Drug Utilization to Risk Minimization

Pharmacists are uniquely positioned to play a central role in the generation of RWE, and among the six regulatory case studies referenced by the EMA reflection paper, two directly concern everyday pharmacy practice, namely the description of drug utilization patterns, including indications, dose, duration, and adherence, as well as the conduct of post-marketing surveillance and the evaluation of the effectiveness of risk minimization measures. Beyond the traditional functions of dispensing and procurement, pharmacists also contribute to data quality and interoperability, ensuring that prescribing and dispensing information captured at the point of care is reliable and usable for regulatory-grade evidence.

Moreover, their participation in the HTA process and regional governance processes places them at the intersection of clinical practice and policymaking, where RWE plays an increasingly decisive role. Their proximity to the patient and involvement in therapy management further strengthen this role, positioning pharmacists as essential actors in observational research.

In a healthcare system increasingly oriented toward value and safety, pharmacists' contributions to RWE generation can support regulatory evaluations, improve therapeutic appropriateness, and inform evidence-based decision-making at both regional and national levels. This evolving role extends beyond traditional dispensing and procurement and requires strengthened competencies in pharmacoepidemiology, data governance, interoperability, and applied analytics (including causal inference and statistical programming), enabling pharmacists to act as methodological stewards of RWE generation.

In line with these considerations, the third report "Real-World Evidence Framework to Support EU Regulatory Decision Making" on the advancements of RWE to promote EU regulatory decisions, published by EMA (14), reported that, in the previous year, among 59 real-world studies coordinated by EMA, 42% focused on drug utilization, 24% on drug safety and 24% on disease epidemiology. This means that two-thirds of studies concerned activities inextricably linked to drugs and pharmacists, highlighting their key role in the management of RWD, generating RWE.

For instance, drug utilization research, aiming to understand how patients take their medications, whether they adhere to their prescribed treatments or how long they take their therapy (persistence), represents an area of research in which pharmacists play an important role. First, they can systematically track each drug dispensing; in addition, thanks to computerized systems, pharmacists can access patients' entire drug history, allowing them to derive drug utilization indicators.

Various international working groups are interested in this field, and in Italy, as part of the FORIERO group (hospital pharmacists for independent research in the economic field, rational use of technology, and outcome evaluation), we are involved in conducting several drug utilization studies in RW covering different therapeutic areas (e.g., oncohematology) (15). One of these, "The Multi-Bio drugs" study, aims to evaluate how biological drugs are used in different therapeutic indications concerning rheumatology, dermatology, and gastroenterology (i.e., Inflammatory Bowel Disease). To date, out of 12 Italian regions involved in the project, 21 hospitals and community pharmacies were recruited to share their RWD on biological drug use, to generate and analyze RWE concerning treatment adherence and persistence, therapy switching, and treatment-related costs.

Challenges Ahead: Culture, Capacity, and Change

Although enthusiasm for RWE is growing, its broader adoption is still hindered by the tendency of clinicians and policymakers to privilege RCTs and perceive RWD as anecdotal, by the limited technical expertise available in non-academic institutions to design and analyze causal OS, and by the considerable investments in IT, personnel, and education required to meet EMA standards; overcoming these challenges will depend on coordinated efforts among academic institutions, healthcare providers, professional associations, and regulators, with a crucial role for pharmacists, whose up-skilled training in data science, epidemiology, and regulatory methods (e.g., TTE and pragmatic designs) will be pivotal to deliver regulatory-grade evidence.

Conclusions

The updated EMA Reflection Paper outlines an ambitious roadmap for integrating RWE into regulatory science, endorsing TTE as a structured method to improve causal inference and generate reliable evidence on drug effectiveness and safety when RCTs are not feasible. To realize this potential, investment in methodological training and cultural change is essential, offering clinical researchers, particularly in pharmacy and health services, both a challenge and an opportunity to transform RWD into trusted evidence for better patient outcomes.

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