Targeting interleukins: An approach for management of inflammatory skin diseases



Aakanchha Jain*, Dimpal Suthar, Shruti Patil
National Institute of Pharmaceutical Education and Research, Ahmedabad
Email: jainaakanchha83@gmail.com

Abstract
Inflammatory skin diseases (ISDs) are a group of skin diseases that are a result of an immunological reaction or autoimmunity. They are characterized by the production of cytokines like interleukins (ILs). Such disorders include acne, psoriasis, vitiligo etc. Studies have concluded that the significant role of various ILs in the majority of ISDs makes it a highly potent target for treatment. This article outlines various available therapies, presents challenges in targeting ILs, novel targeting approaches and upcoming possibilities for effective management of ISDs.

Keywords: Interleukins, inflammation, skin diseases

1. Introduction

1.1. Inflammatory skin diseases

ISDs are characterized by the production of proinflammatory cytokines, resulting in activation of innate and adaptive immunity. These are categorized as autoimmune and autoinflammatory diseases. Autoimmune disease like lupus erythematosus, Sjögren's syndrome, and vitiligo involves the roles of B and T cells in errant responses to autoantigen and autoantibodies. Whereas autoinflammatory skin diseases result in tissue damage due to activation of innate immune cells like neutrophils, natural killer cells, and mast cells. Few diseases involve both components, autoinflammatory and autoimmune, such as psoriasis, lichen planus, and allergic contact dermatitis (1,2).

1.2. Interleukins & their role in inflammatory skin disorders

ILs are a class of cytokines that are produced by various cells of the body, like leukocytes. Alteration in expression of ILs can cause proliferation, differentiation and activation to modulate during immune responses and inflammation (3,4). They play a significant role in the pathogenesis of ISDs like psoriasis and lupus erythematosus. Psoriasis is a chronic relapsing autoimmune disorder characterized by silvery scales, dryness and inflamed skin. IL-1α and IL-1β have been known to be a part of early pathogenesis in psoriasis. The expression level of protein of IL-36γ are higher in psoriasis as compared to other ISDs like atopic dermatitis (AD), eczema, etc. The missense mutation in a gene coding for IL-36 Ra results in decreased production of IL-36, this deficiency causes the generation of pustular psoriasis (5,6). IL-17 produced by neutrophils, is one of the most studied pro-inflammatory cytokines that has been associated with several pathways in the pathogenesis of skin diseases mediated by immune responses, including vitiligo, psoriasis, lichen planus and acne. Presence of neutrophils in skin biopsy samples of ISDs like psoriasis and pyoderma gangrenosum (PG) confirms the role of IL-17 and neutrophil activity in such disorders. Further, IL-6 and IL-8 are neutrophil-activating cytokines induced by IL-17, thus aggravating the severity of the disease. IL-23 levels are found to be elevated in PG and AD. Also, in vivo studies on the mouse model suggest that upregulation of

IL-25 (IL-17E) in AD causes the release of endothelin-1, resulting in pruritus development. Nonetheless, IL-17 can also serve as a marker of the disease severity in conditions like erosive lichen planus and systemic lupus erythematosus (7,8).

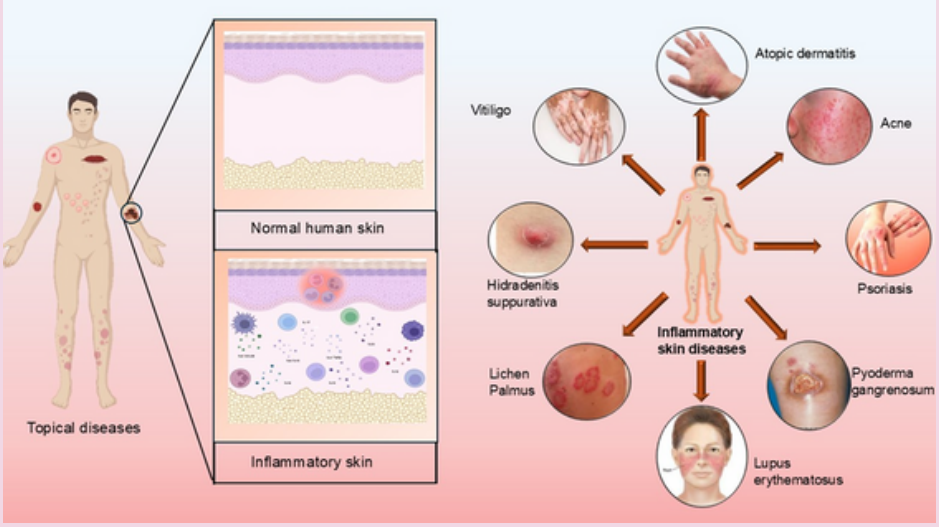

Figure 1. Types of IL- IL-associated IS

2. Available treatment for targeting interleukins

Over the years, research and clinical trials have concluded that ILs are a promising therapeutic target for effective management of ISDs. The major section of therapies targeting ILs consists of monoclonal antibodies (mAbs). Treatment options other than anti-ILs therapy include corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs) and pulsed laser therapies. Though all these therapies have a significant effect on reducing the disease severity, but present side effects like telangiectasia, teratogenicity, bone marrow suppression etc. (9). Several IL inhibitors are available in the market. Approved mAbs for AD include dupilumab (inhibitor of IL-4Ra) and tralokinumab (inhibitor of IL-13). Tozorakimab, fezakinumab, and eblasakimab are a few agents explored under clinical trials for AD. Similarly, mAbs for the treatment of psoriasis include ustekinumab, secukinumab, brodalumab and so on (10). Majorly, agents acting on IL-23/IL-17 axis are widely explored and an effective treatment option for psoriasis; secukinumab, ixekizumab, briakinumab and risankizumab are examples of approved agents, to name a few (11). Further IL-1 (IL-1α and IL-1β) inhibiting agents such as anakinra, canakinumab and rilonacept are also dominant in the market with wider application in skin conditions including inflammation like Schnitzler syndrome, hidradenitis suppurativa and Sweet's syndrome. Gevokizumab is a novel IL-1 inhibitory agent that is in the clinical trial stage for the treatment of acne (12).

3. Challenges in interleukins targeted drug delivery

Despite the therapeutic potential of IL-targeted drug delivery in ISDs, it faces several challenges such as skin barrier penetration, off-target effects, and drug stability.

3.1. Physical barrier and skin environment

Inflammation causes edema and altered tissue structure of the skin. Further inflammatory skin environments are chemically hostile, characterized by elevated protease activity, oxidative stress, acidic pH, and increased immune cell infiltration which can rapidly degrade biologics in diseases like AD. These pathological changes hinder the topical delivery of the ILs-targeted agents which are usually hydrophilic large molecules (9). The inflammatory process itself can also lead to changes in the expression and availability of target molecules, affecting the effectiveness of the inhibitors (13).

For example, Secukinumab, an IL-17A inhibitor used in psoriasis, must be administered subcutaneously because it cannot penetrate thickened SC. However, lower drug loading and patient acceptability are challenges in approaches explored to deliver secukinumab topically (14). Another example is Ixekizumab which has protein structure that makes it susceptible to enzymatic degradation by protease in the body, contributing to their metabolic clearance and relatively shorter half-lives compared to other biologics (7).

3.2. Challenges in systemic drug delivery

Systemic administration can lead to widespread immunosuppression, increasing the risk of infections and other systemic side effects. Dupilumab, an IL-4 and IL-13 inhibitor used in the treatment of AD, must be administered via the subcutaneous route. It has high systemic side effects such as conjunctivitis, oral herpes, and cold sores on the mouth/lips (15).

3.3. Formulation related challenges

Proper folding is critical for antibody function, and aggregation is the most frequent issue in mAbs, impacting both potency and safety of treatments. To address this, several strategies are employed, including glycosylation, modifying protein charge, and rationally designing antibodies to eliminate aggregation-prone regions. Moreover topical vehicles like gels or creams may affect structural integrity and activity (16).

4. Novel targeting approaches

Systemic delivery of IL-targeted therapeutic agents like mAbs may lack specificity and cause systemic toxicity. Novel targeted drug delivery approaches that focus on IL modulation can enhance the treatment precision and minimize systemic side effects (Table 1).

Table 1. Novel targeting approaches focusing on IL modulation

S. No.	Targeting Approach	Drug	Formulation	Remarks	Ref
1	Amphiphilic lipid nanocarrier	Erlotinib and IL36 siRNA	Topical delivery of IL36 siRNA with erlotinib in psoriasis by using novel amphiphilic lipid augments	The delivery of erlotinib and IL36 siRNA was increased by developing the cationic lipid nanocarrier, which disrupts the stratum corneum layer of the skin.	(17)
2	Thermoresponsive Polymeric Dexamethasone Prodrug	Dexamethasone	N- (2-hydroxypropyl) methacrylamide (HPMA) copolymer based thermoresponsive dexamethasone prodrug (ProGel-Dex)	The ProGel-DEX has shown improved efficacy and safety in treating psoriasis as compared to topical dexamethasone treatment	(18)
3	Nanoemulsion	Pioglitazone	nanoemulsion of pioglitazone (PGZ) as a topical cream	This formulation significantly reduced inflammatory cytokines (IL-6, IL-1β, TNF-α) and improved stratum corneum structure. Histopathology revealed decreased dermal thickness and inflammatory cell infiltration in atopic dermatitis.	(19)
4	Nanocapsules	Cycosporin-A	PLGA nanocarriers were prepared by solvent displacement method for atopic dermatitis	Cyclosporin A showed enhanced penetration into deeper skin layers and reduced pro-inflammatory cytokine levels. IL-6 and IL-8 levels decreased by ~50%, highlighting strong anti-inflammatory activity.	(20)

5	novel self-diffusible polymeric nanoparticle loaded in silk fibrin hydrogel	curcumin	Curcumin was encapsulated in self-assembled polymeric nanoparticles formed from RRR-α-tocopheryl succinate-grafted ε-polylysine (VES-g-ε-PLL) conjugates.	The positively charged nanoparticles enhanced skin penetration and, when incorporated into a silk fibroin hydrogel, diffused into deeper layers. In vivo studies confirmed significant reductions in TNF-α, NF-κB, and IL-6 levels.	(21)
6	Micellpelex	siRNA	Micellpelex consisted of tri block micelles (poly (ethylene glycol)-b-poly (L-lysine)-b-poly (L leucine) (PEG-PLL-PLLeu)	The prepared micelles demonstrated high transfection efficiency, no cytotoxicity, effective DNA condensation, and lysosomal escape, making them efficient nonviral gene delivery vectors. They successfully knocked down Rel expression, reducing IL-23 and IL-17 levels.	(22)
7.	Chitosan-based NPs	hydrocortisone (HC) and hydroxytyrosol (HT)	Chitosan nanoparticles were prepared by the ionic cross-linking method	Co-loaded nanoparticles of hydrocortisone and hydroxytyrosol demonstrated enhanced skin accumulation,reduced systemic permeation, and improved therapeutic outcomes in atopic dermatitis. This delivery system offers a promising approach for effective and safer topical treatment.	(23)
8.	Dual targeting fusion protein (DTF)	Anti- IL-17A scFv/ sTNFR1-Fc	DTF is generated with an anti-IL-17 A single chain variable fragment, a soluble TNF receptor 1, and a 32-amino-acid linker which was used to join the two parts.	The prepared fusion protein was found to be more potent thanetanercept in ameliorating psoriasis. It reduces the expression of keratin in psoriasis like skin in mice.	(24)
9.	Polymeric nanoparticles	Isotretinoin	Isotretinoin-delonix polymeri nanoparticles by nanoprecipitation method	The polymeric nanoparticles shows 3 fold higher accumulation of drug in hair follicles compared to plain drug solution, acts on IL-6 expression and reduced the photo irritation	(25)

4.1. Vesicular system

Vesicular delivery systems, including liposomes, niosomes, transferosomes and ethosomes are emerging as effective platforms for delivering ILs inhibitors. These nanocarriers can encapsulate both hydrophilic and lipophilic drugs, protecting sensitive biologics like mAbs or cytokine inhibitors from degradation. Their lipid-based composition allows for enhanced interaction with the skin barrier, improving the penetration through the SC and facilitating targeted delivery to inflamed tissues. In diseases such as psoriasis and AD, vesicular systems can localize the action of ILs inhibitors at the site of inflammation, thereby minimizing the systemic exposure and associated side effects (26).

4.1.1. Lipid nanoparticles

Among various lipid-based carrier systems, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are considered highly effective for dermal drug delivery. Their small particle size and high lipid content allow them to adhere closely to the skin, forming a uniform, occlusive film over the SC. This film enhances skin hydration and improves drug retention at the application site. Additionally, incorporating the drug within the lipid matrix enhances its chemical stability by protecting it from degradation and minimizing leaching. These systems also offer favorable aesthetic characteristics like their opaque appearance, smooth texture, and fluid consistency. This results in a light, non-greasy skin feel, making them more comfortable and appealing for patients, which is especially important for long-term use in chronic ISDs (27).

4.1.2. Microneedles (MNs)

MNs offer a promising strategy for delivering biologics in ISDs by overcoming the barrier posed by the SC. They create microchannels that allow large biomolecules, such as IL inhibitors, to penetrate directly into the epidermis and dermis, where inflammation is active. Additionally, MNs can be designed using biodegradable materials that protect biologics from degradation in the hostile inflamed environment. Their minimally invasive, painless nature makes them patient-friendly, encouraging better adherence (28).

4.1.3. Polymeric nanoparticles

Polymeric nanoparticles are highly promising carriers due to their customizable properties and biocompatibility. Their size, shape, surface charge, and composition can be precisely engineered to deliver fragile mAbs which allows for enhanced stability, prolonged release, and targeted accumulation at inflamed sites. Their biodegradability further reduces long-term toxicity risks. Additionally, control over polymer chemistry and supramolecular assembly enables the design of stimuli-responsive systems that can release biologics in response to skin-specific triggers like pH or enzymes. These features make polymeric nanoparticles a robust platform for localized, sustained, and safe delivery of biologics in chronic ISDs (29).

4.2. Hydrogel

A hydrogel is a 3-D network of hydrophilic polymers that can absorb and retain a large amount of water. The long-term systemic administration of IL-targeting biologics poses a greater risk of adverse effects compared to topical treatments. The biologics entrapped hydrogels facilitate the delivery of the drug directly to the affected skin areas in a controlled manner. The added advantage of hydrogel is that it allows the maintenance of the structural integrity of biological and large molecules (30).

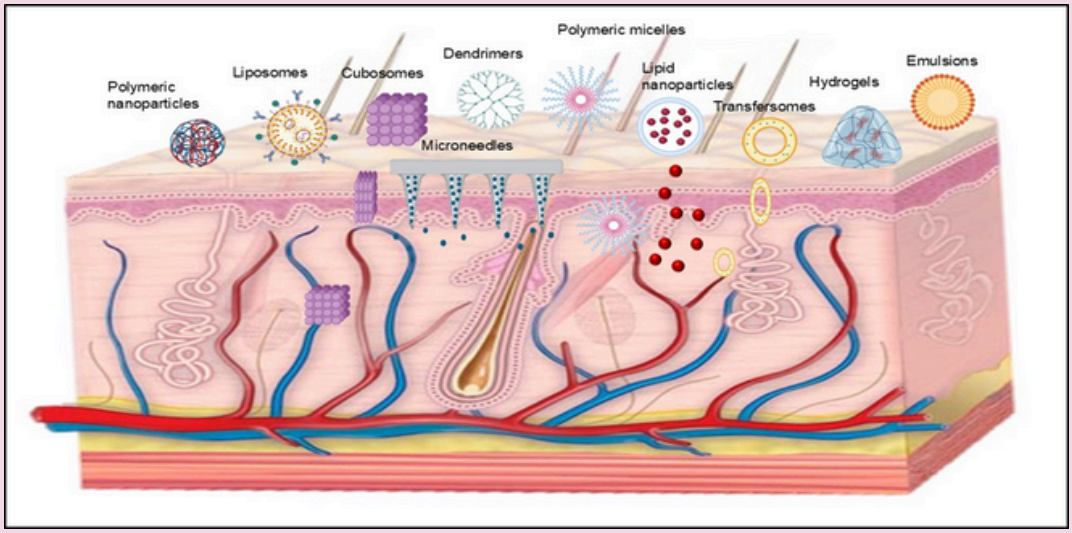

Figure 2. Drug Delivery approaches for IL targeted therapy in ISDs

5. Future prospects

Current treatment modalities use single agent for treatment of ISDs. But the complexity of immune system, which includes several signalling pathways demands for targeting multiple ILs. Targeting multiple ILs would provide synergistic effects. One such example is Sanofi's tetravalent bispecific tandem immunoglobulin that inhibits both IL-4 and IL-13. Such agents open window for new opportunities to explore dual effect that is both systemic and local effects. However, use of fixed combination drugs may be complex to study the effect of single drug on treatment (30).

6. Conclusion

ILs are crucial part of pathogenesis of ISDs, making then promising target for therapeutic intervention. Current treatment strategies have certain barriers like stability issue and systemic side effects, also targeted delivery is challenging. These issues can be resolved by employing discussed novel drug delivery. However, research and advancements in the therapeutic agents and their delivery systems are encouraged to improve IL-targeted therapy and quality of life of patients with ISDs.

References

1. Mesas-Fernández A, Bodner E, Hilke FJ, Meier K, Ghoreschi K, Solimani F. Interleukin-21 in autoimmune and inflammatory skin diseases. Eur J Immunol. 2023;53(4):1–12.
2. Sheida Naderi-Azad, medical student, University of Toronto Faculty of Medicine, Toronto, ON C. DermaNet. Inflammasomes and inflammatory skin diseases. Available from: https://dermnetnz.org/topics/inflammasomes-and-inflammatory-skin-diseases
3. Weiss E, Mamelak AJ, La Morgia S, Wang B, Feliciani C, Tulli A, et al. The role of interleukin 10 in the pathogenesis and potential treatment of skin diseases. J Am Acad Dermatol. 2004;50(5):657–75.
4. Angel A. Justiz Vaillant; Ahmad Qurie. Interleukin [Internet]. StatPearls. StatPearls Publishing LLC; Available from: https://www.ncbi.nlm.nih.gov/books/NBK499840/
5. Buhl A lena, Wenzel J. Interleukin-36 in Infectious and Inflammatory Skin Diseases. 2019;10(May):1–11.
6. D LC, Fiocco Z, Satoh TK, Peris K, French LE, Calabrese L. Therapeutic potential of targeting interleukin-1 family cytokines in chronic inflammatory skin diseases *. 2022;10(Table 2):925–41.
7. Speeckaert R, Lambert J, Grine L, Van Gele M, De Schepper S, van Geel N. The many faces of interleukin-17 in inflammatory skin diseases. Br J Dermatol. 2016;175(5):892–901.
8. Beelen AJ Van, Teunissen MBM, Kapsenberg ML, Jong EC De. Interleukin-17 in inflammatory skin disorders. 2007;(II):374–81.
9. Guo JW, Jee SH. Strategies to develop a suitable formulation for inflammatory skin disease treatment. Int J Mol Sci. 2021;22(11).
10. Bieber T. Disease modification in inflammatory skin disorders: opportunities and challenges. Nat Rev Drug Discov. 2023;22(8):662–80.
11. Tsai YC, Tsai TF. Anti-interleukin and interleukin therapies for psoriasis: current evidence and clinical usefulness. Ther Adv Musculoskelet Dis. 2017;9(11):277–94.
12. Fenini G, Contassot E, French LE. Potential of IL-1, IL-18 and inflammasome inhibition for the treatment of inflammatory skin diseases. Front Pharmacol. 2017;8(MAY):1–20.
13. Raina N, Rani R, Thakur VK, Gupta M. New Insights in Topical Drug Delivery for Skin Disorders: From a Nanotechnological Perspective. ACS omega. 2023 Jun;8(22):19145–67.
14. Type I, Gazala I. The development of a liposomal form Secukinumab – an IL 17 pathway inhibitor in the treatment of psoriasis. 2025;
15. Hemrajani C, Negi P, Parashar A, Gupta G, Jha NK, Singh SK, et al. Overcoming drug delivery barriers and challenges in topical therapy of atopic dermatitis: A nanotechnological perspective. Biomed Pharmacother. 2022;147:112633.
16. Stevens N, Cowin A. Overcoming the challenges of topical antibody administration for improving healing outcomes: a review of recent laboratory and clinical approaches. Wound Pract Res. 2017;25:188.

17. Boakye CHA, Patel K, Doddapaneni R, Bagde A, Marepally S, Singh M. Novel amphiphilic lipid augments the co-delivery of erlotinib and IL36 siRNA into the skin for psoriasis treatment. J Control release Off J Control Release Soc. 2017 Jan;246:120–32.
18. Jiang H, Fu X, Zhao G, Du X, Georgesen C, Thiele GM, et al. Intradermal Injection of a Thermoresponsive Polymeric Dexamethasone Prodrug (ProGel-Dex) Ameliorate Dermatitis in an Imiquimod (IMQ)-Induced Psoriasis-like Mouse Model. Mol Pharm. 2024;21(10):4995–5004.
19. Espinoza LC, Silva-Abreu M, Calpena AC, Rodríguez-Lagunas MJ, Fábrega MJ, Garduño-Ramírez ML, et al. Nanoemulsion strategy of pioglitazone for the treatment of skin inflammatory diseases. Nanomedicine. 2019 Jul;19:115–25.
20. Badihi A, Frušić-Zlotkin M, Soroka Y, Benhamron S, Tzur T, Nassar T, et al. Topical nano-encapsulated cyclosporine formulation for atopic dermatitis treatment. Nanomedicine. 2020 Feb;24:102140.
21. Mao KL, Fan ZL, Yuan JD, Chen PP, Yang JJ, Xu J, et al. Skin-penetrating polymeric nanoparticles incorporated in silk fibroin hydrogel for topical delivery of curcumin to improve its therapeutic effect on psoriasis mouse model. Colloids Surf B Biointerfaces. 2017 Dec;160:704–14.
22. Fan T, Wang S, Yu L, Yi H, Liu R, Geng W, et al. Treating psoriasis by targeting its susceptibility gene Rel. Clin Immunol. 2016 Apr;165:47–54.
23. Hussain Z, Katas H, Mohd Amin MCI, Kumolosasi E, Buang F, Sahudin S. Self-assembled polymeric nanoparticles for percutaneous co-delivery of hydrocortisone/hydroxytyrosol: an ex vivo and in vivo study using an NC/Nga mouse model. Int J Pharm. 2013 Feb;444(1–2):109–19.
24. Liu Z, Liu H, Xu P, Yin Q, Wang Y, Opoku YK, et al. Ameliorative effects of a fusion protein dual targeting interleukin 17A and tumor necrosis factor α on imiquimod-induced psoriasis in mice. Biomed Pharmacother [Internet]. 2018;108:1425–34. Available from: https://www.sciencedirect.com/science/article/pii/S0753332218352211
25. Ogunjimi AT, Chahud F, Lopez RF V. Isotretinoin-Delonix polymeric nanoparticles: Potentials for skin follicular targeting in acne treatment. Int J Pharm [Internet]. 2021;610:121217. Available from: https://www.sciencedirect.com/science/article/pii/S0378517321010231
26. Gupta M, Udita A, and Vyas SP. Nanocarrier-based topical drug delivery for the treatment of skin diseases. Expert Opin Drug Deliv. 2012 Jul;9(7):783–804.
27. Arora R, Sameer S. K, Varun K, and Jain S. Solid lipid nanoparticles and nanostructured lipid carrier-based nanotherapeutics in treatment of psoriasis: a comparative study. Expert Opin Drug Deliv. 2017 Feb;14(2):165–77.
28. Han Y, Qin X, Lin W, Wang C, Yin X, Wu J, et al. Microneedle-Based Approaches for Skin Disease Treatment. Nano-Micro Lett. 2025;17(1):132.
29. Elsabahy M, Wooley KL. Design of polymeric nanoparticles for biomedical delivery applications. Chem Soc Rev. 2012;41(7):2545–61.
30. Cao H, Wang M, Ding J, Lin Y. Hydrogels: a promising therapeutic platform for inflammatory skin diseases treatment. J Mater Chem B. 2024;12(33):8007–32.

Name: _____

Contributing Factors to Inflammation

N Q B R U V T L E R F N P P E A V S Y Z
S T T D A F E Y V H Z D V K P F X T H C
S A S V S J M S P E J E V W F S L Z X N
K W W K B X E H B H G K R Q W B Z J P O
F S C V R L C K T A X O B E A B N B L I
Y A D I E T O T V Y I J V P S U R K Y T
P S J Y M U L L T H A M P Z H N E B X C
I X O N T K H E K S T Y P G J V U K L A
P U X I K I Z X T Y A E S U Y Y F W Z E
G G W M U Y S R X G J T P G F E I W E R
L N L S Y S E E U K N K Q S K A M H P E
T B O V B S Y Q B M Y I N F E C T I O N
R A T D S M N R W O S H K F V A F T X U
N H Z E Q K X S U G J A Z O V N H N D M
K C G R E N Y H R J J L L V M B R O Z M
K M Y A M H O R M O N E S P O S J F O I
B A U V C D K E I J A I D M O G L X C O
E F K W N O V B E Y W S N A H E R R I T
Z M Z T R X Y N J A S F B A Z B N J Z U
E L Y T S E F I L Y R A T N E D E S X A

AGE
AUTOIMMUNE REACTION
DIET
HORMONES
INFECTION
INJURY
NEOPLASM
OBESITY
SEDENTARYLIFESTYLE
SMOKING
STRESS

Answers on Page 100