**Supplementary Table S1: Pathway, type, effect and characteristics of biologics used off-label for skin disorders**

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| **IL-1** |
| **Role in health** | **Role in skin disease** | **Immunological effects** |
| - Major mediator of innate immune response | - Crucial trigger of autoinflammatory diseases | - Induction of IL-1 target genes (IL-6, IL-8, MCP-1, COX-2…) (1) |
| Biologic | Type | Differences between biologics |
| Anakinra | Recombinant IL-1 receptor antagonist | - Anakinra competes with IL-1α and IL-1β to bind to the IL-1 receptor. - Canakinumab inhibits IL-1β and has a longer half-life (26d) compared to anakinra (4-6h) (2).  |
| Canakinumab | Monoclonal antibody (MoAb) against IL-1β |
| **IL-17** |
| **Role in health** | **Role in skin disease** | **Immunological effects** |
| - Epithelial barrier defence against fungal infections, candida and bacteria | - Key factor in psoriasis and psoriasis arthritis - Plausible role in neutrophilic disorders | - Acts on non-hematopoietic cells to promote keratinocyte proliferation - initiates a feed-forward amplification loop promoting additional IL-17 signaling (3)- Synergistic effect on other cytokines (e.g. TNF-α) (4) |
| Biologic | Type | Differences between biologics |
| Secukinumab | MoAb against IL-17A | - Secukinumab and ixekizumab inhibit both IL-17A. - Brodalumab inhibits IL-17A, IL-17F, IL-17C and IL-17E  |
| Ixekizumab |
| Brodalumab | MoAb against the IL-17 receptor A subunit |
| **IL-12** |
| **Role in health**  | **Role in skin disease** | **Immunological effects** |
| - Stimulating Th1-mediated immunity (antiviral and antitumoral protection) | - Increased levels are found in psoriasis skin (5), although the contributing role of IL-12 is unclear in psoriasis (6)  | - Stimulates differentiation of naive T cells into Th1 cells- Inducer of IFN-γ in NK cells and T cells (7) |
| Biologic | Type | Differences between biologics |
| Ustekinumab | MoAb against the p40 subunit common to IL-12 and IL-23 | - Ustekinumab interacts with both the Th1 and Th17 pathway by blocking IL-12 and IL-23 |
| **IL-23** |
| **Role in health** | **Role in skin disease** | **Immunological effects** |
| - Regulation of the IL-17 pathway  | - ‘Upstream’ cytokine elevated in psoriasis and other Th17 mediated disorders | - Acts on hematopoietic cells.- Late factor in the differentiation of Th17 cells |
| Biologic | Type | Differences between biologics |
| Guselkumab | MoAb against the p19 subunit of IL-23 | - Anti-p19 antibodies do not inhibit IL-12 which might lead superior efficacy with less adverse events in IL-23/IL-17 mediated disorders such as psoriasis (8) |
| Risankizumab |
| Tildrakizumab |
| **TNF-α** |
| **Role in health** | **Role in skin disease** | **Immunological effects** |
| - Widely present pro-inflammatory cytokine- Protective against infections (9) | - Role in psoriasis, hidradenitis suppurativa and granuloma annulare is evident. | - Stimulates IL-23 production by dendritic cells- Synergises with other cytokines (e.g. IL-17, IFN-γ) (10,11) |
| Biologic | Type | Differences between biologics |
| Adalimumab | MoAb against TNF-α | - Most data are available for adalimumab and etanercept. - The lack of an Fc-region in certolizumab pegol minimizes complement and antibody dependent cell-mediated cytotoxicity and active transfer over the placenta (12)- Infliximab is administered intravenously (>< subcutaneously) and is less frequently used in dermatology. |
| Infliximab |
| Certolizumab Pegol | MoAb, Fc-free, PEGylated, against TNF-α |
| Etanercept | TNF receptor linked to the Fc portion of human IgG1 |
| **IgE** |
| **Role in health** | **Role in skin disease** | **Immunological effects** |
| - Eradication of parasitic infections | - Allergy and urticaria- Bullous pemphigoid | - Mast cell degranulation- Eosinophil chemotaxis |
| Biologic | Type | Differences between biologics |
| Omalizumab | MoAb against IgE | - Omalizumab binds stronger to free IgE than the high affinity IgE receptor (13) |

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