Systematic Review of the efficacy, safety and management considerations of tofacitinib: Emerging evidence and key clinical considerations for JAK-inhibitor use in dermatology

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Introduction

- Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling has emerged as a novel target for immune-mediated and inflammatory diseases (IMIDs) (Figure 1). Tofacitinib, a first generation JAK inhibitor, is currently the most studied JAK-inhibitor for cutaneous-disease.

Objective

- Review the efficacy, safety and monitoring requirements of tofacitinib in CPP, AA, AD and vitiligo.

Methods

- Systematic review of Pubmed/Medline.
- Papers from the last 10 years were considered (Figure 2).

Figure 2. Outcome of literature search

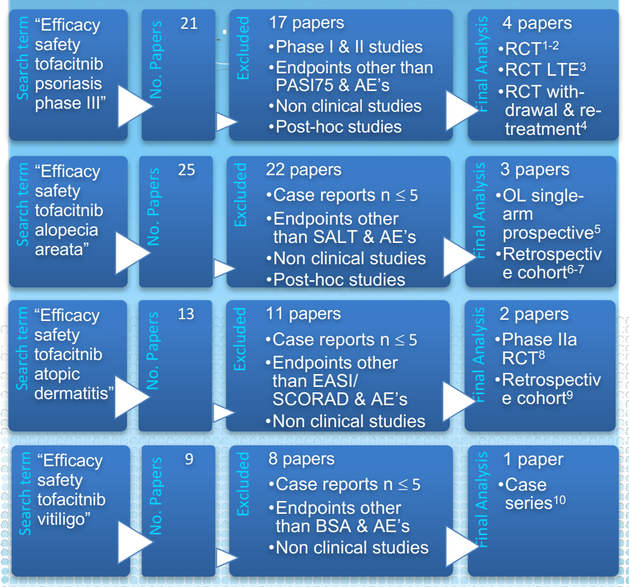
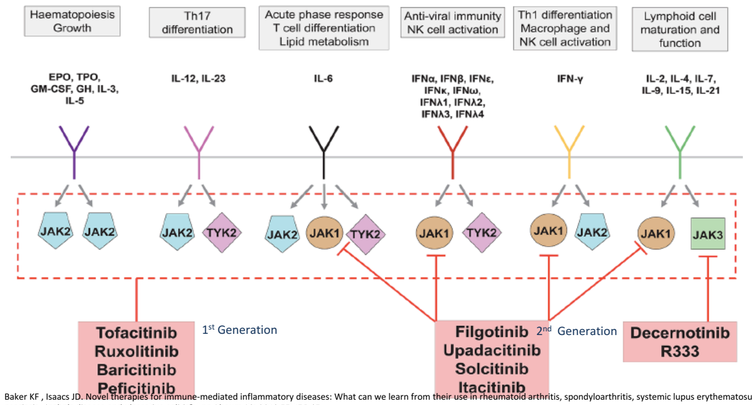


Figure 1. Overview of Janus kinase (JAK) inhibitors developed for the treatment of IMIDs



Baker KF , Isaacs JD. Novel therapies for immune-mediated inflammatory diseases: What can we learn from their use in rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, psoriasis, Crohn's disease and ulcerative colitis? Ann Rheum Dis 2018;77:175-87.

Tofacitinib is a first generation pan-JAK inhibitor which preferentially inhibits JAK1and 3. Second generation JAK inhibitors exert a selective blockade of JAK1 or JAK3 with less risk of haematopoietic toxicity (JAK2 inhibition).

Results:

Table 1. Efficacy of tofacitinib for CPP in adults with moderate to severe CPP (PASI ≥ 12) : Outcomes from phase 3 RCT's

	(N)	% achieved PASI75
Papp et al. 2015 BJD [1]	1861	42.9 (tofa 5mg BD, wk16) 59·4 (tofa 10mg BD,wk16)
Bachelez et al. 2015 Lancet [2]	1106	39·5 (tofa 5mg BD, wk12) 63·6 (tofa 10mg BD, wk12); **P<0·001 v etanercept* 58·8 (etanercept, wk12) 5.6 (placebo, wk12)
Papp et al. 2016 JAAD [3]	1861	55.6 (tofa 5mg BD, wk28) 68.8 (tofa 10mg BD, wk28) 74.1 and 79.4, maintained PASI75 to week 52
Bissonnette et al. 2015 BMJ [4]	666	43.8 (tofa 5mg BD, wk24) 67.6 (tofa 10mg BD, wk24 *Relapse on withdrawal* 67.2 (tofa 5mg BD to placebo)* 57.1 (tofa 10mg BD to placebo)* *Median time to loss of PASI75: 8wk

Table 2. Efficacy of tofacitinib (5mg BD) for severe AA (≥50% scalp loss) in adults and adolescents

	(N)	% improvement in SALT
Kennedy Crispin et al. 2016 JCI Insight[5]	66	32 (≥50% improvement) 32 (5-50% improvement) 36 (< 5% improvement) *Time to relapse: 8.5 weeks*
Liu et al. 2017 JAAD [6]	65	20.0 (≥ 90% improvement) 38.4 (51- 90% improvement) 18.5 (6-50% improvement) 23.1 (≤ 5% improvement) *4-18 months of tofacitinib Rx* *Relapse during Rx: 8/65 (12.3%)*
Craiglow et al. 2017 JAAD [7]	13 Adoles-cents (12-17 years)	61

Table 3. Efficacy of tofacitinib for AD

	N (baseline severity)	% improvement EASI/SCORAD
Bissonnett et al.[8]	69 (Mild-Mod)	81.7 (tofa 2% top BD, 4wk) 29.9 (vehicle top BD, 4wk)
Levy et al. 2015[9]	6 (Mod-severe)	54.9 (tofa 5mg BD, 0-14wk) 66.6 (tofa 5mg BD,8-29wk)

Table 4. Efficacy of tofacitinib for vitiligo

	N	Mean % re-pigmenation
Liu et al. [10]	10	5.4 (of the 5/10 responders)

Table 5. Pooled analysis of adverse events and laboratory abnormalities associated with tofacitinib treatment for CPP, AA, AD and vitiligo

Serious AE's / AE's of special interest	n/N (%)
SAE's	42/2036 (2.1)
Serious infections	14/2922 (0.5)
Herpes zoster/simplex/CMV	54/3053 (1.5)
NMSC	12/3588 (0.4)
Malignancy ex NMSC	1.2/3588 (0.4)
Major cardiac events	5/2482 (0.8)
GIT perforation	2/666 (0.3)
Common AE's	
Nasopharyngitis	189/2076 (9)
URTI	36/154 (23)
Headache	70/1108 (6.3)
Fatigue	8/131 (6)
Laboratory abnormalities	
CK elevation	787/2991 (26)
Dyslipidaemia	211/2987 (7)
Cytopenias	0.7/65 (1)
Elevated transaminases	10/88 (11)

Conclusion

For the treatment of CPP, tofacitinib 10mg PO BD has comparable to superior efficacy than available systemics. Evidence for tofacitinibs' efficacy in AA is stronger than for currently used systemics, which have not been subject to prospective trials. Topical tofacitinib was efficacious in mild-moderate AD and has the advantage of being steroid sparing, but TCS comparators are lacking. Evidence for its use in vitiligo is lacking at present. Development of more "selective" JAK1/3 inhibitors, with theoretically less risk of hematopoietic toxicity, is presently being favored in clinical trials. Tofacitinib has a relatively good safety profile, but herpes reactivation and asymptomatic CK elevations are common. Hb and lipid profile monitoring has been advocated.

References

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JAK: Janus kinase, **STAT:** signal transducer and activator of transcription, **IMIDs:** immune-mediated and inflammatory diseases, **CPP:** chronic plaque psoriasis, **AD:** atopic dermatitis, **AA:** alopecia areata, **SALT:** Severity of Alopecia Tool, **SAE:** serious adverse events